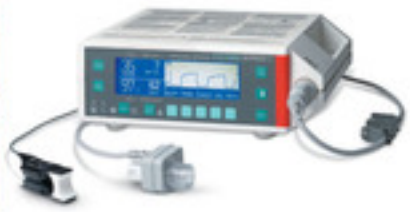
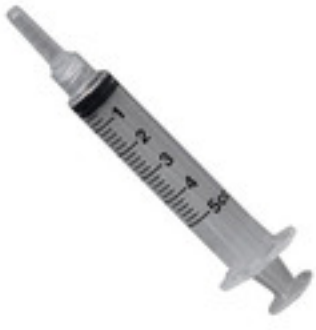



SAFE MEDICAL DEVICES FOR CHILDREN

INSTITUTE OF MEDICINE
OF THE NATIONAL ACADEMIES






SAFE MEDICAL DEVICES FOR CHILDREN

Committee on Postmarket Surveillance of Pediatric Medical Devices

Board on Health Sciences Policy

Marilyn J. Field and Hugh Tilson, *Editors*

INSTITUTE OF MEDICINE
OF THE NATIONAL ACADEMIES

THE NATIONAL ACADEMIES PRESS
Washington, DC
www.nap.edu

THE NATIONAL ACADEMIES PRESS • 500 Fifth Street, N.W. • Washington, DC 20001

NOTICE: The project that is the subject of this report was approved by the Governing Board of the National Research Council, whose members are drawn from the councils of the National Academy of Sciences, the National Academy of Engineering, and the Institute of Medicine. The members of the committee responsible for the report were chosen for their special competences and with regard for appropriate balance.

This study was supported by Contract No. 223-01-2460, Task Order No. 11 between the National Academy of Sciences and the U.S. Food and Drug Administration. Any opinions, findings, conclusions, or recommendations expressed in this publication are those of the author(s) and do not necessarily reflect the view of the organizations or agencies that provided support for the project.

Library of Congress Cataloging-in-Publication Data

Institute of Medicine (U.S.). Committee on Postmarket Surveillance of Pediatric Medical Devices.
Safe medical devices for children / Committee on Postmarket Surveillance of Pediatric Medical Devices, Board on Health Sciences Policy ; Marilyn J. Field and Hugh Tilson, editors ; Institute of Medicine of the National Academies.— 1st ed.
p. ; cm.
"This study was supported by Contract No. 223-01-2460, Task Order No. 11 between the National Academy of Sciences and the U.S. Food and Drug Administration."
ISBN 0-309-09631-6 (hardcover)
1. Pediatrics—Equipment and supplies—Standards—United States. 2. Pediatrics—United States—Equipment and supplies—Evaluation.
[DNLM: 1. Product Surveillance, Postmarketing—standards—Child—United States. 2. Equipment Safety—standards—Child—United States. 3. Equipment and Supplies—standards—Child—United States. WS 26 I61s 2005] I. Field, Marilyn J. (Marilyn Jane) II. Tilson, Hugh Hanna. III. Title.
RJ34.I57 2005
362.198'92—dc22
2005024875

Additional copies of this report are available from the National Academies Press, 500 Fifth Street, N.W., Lockbox 285, Washington, DC 20055; (800) 624-6242 or (202) 334-3313 (in the Washington metropolitan area); Internet, http://www.nap.edu.

For more information about the Institute of Medicine, visit the IOM home page at: **www.iom.edu**.

Printed in the United States of America

The serpent has been a symbol of long life, healing, and knowledge among almost all cultures and religions since the beginning of recorded history. The serpent adopted as a logotype by the Institute of Medicine is a relief carving from ancient Greece, now held by the Staatliche Museen in Berlin.

Front Cover Photographs:
Top row, second from left: CO2SMO® Capnograph/Pulse Oximeter (Used with permission of Respironics, Inc., Murrysville, PA).
Top row, fourth from left: SJM Regent® Valve (Courtesy of St. Jude Medical, Inc.).
Second row, second from left: Vertical Expandable Prosthetic Titanium Rib (VEPTR) (Courtesy of Robert M. Campbell, M.D., Thoracic Institute, CHRISTUS Santa Rosa Children's Hospital).
Second row, fourth from left: Auria BTE Processor (Courtesy of Advanced Bionics Corporation).
Third row, first from left: Medtronic Paradigm® 515 insulin pump and Paradigm Link™ monitor (Reproduced with permission of Medtronic, Inc.).
Third row, fourth from left: Courtesy of the National Center on Physical Activity and Disability.

"Knowing is not enough; we must apply.
Willing is not enough; we must do."
—Goethe

INSTITUTE OF MEDICINE
OF THE NATIONAL ACADEMIES

Advising the Nation. Improving Health.

THE NATIONAL ACADEMIES

Advisers to the Nation on Science, Engineering, and Medicine

The **National Academy of Sciences** is a private, nonprofit, self-perpetuating society of distinguished scholars engaged in scientific and engineering research, dedicated to the furtherance of science and technology and to their use for the general welfare. Upon the authority of the charter granted to it by the Congress in 1863, the Academy has a mandate that requires it to advise the federal government on scientific and technical matters. Dr. Ralph J. Cicerone is president of the National Academy of Sciences.

The **National Academy of Engineering** was established in 1964, under the charter of the National Academy of Sciences, as a parallel organization of outstanding engineers. It is autonomous in its administration and in the selection of its members, sharing with the National Academy of Sciences the responsibility for advising the federal government. The National Academy of Engineering also sponsors engineering programs aimed at meeting national needs, encourages education and research, and recognizes the superior achievements of engineers. Dr. Wm. A. Wulf is president of the National Academy of Engineering.

The **Institute of Medicine** was established in 1970 by the National Academy of Sciences to secure the services of eminent members of appropriate professions in the examination of policy matters pertaining to the health of the public. The Institute acts under the responsibility given to the National Academy of Sciences by its congressional charter to be an adviser to the federal government and, upon its own initiative, to identify issues of medical care, research, and education. Dr. Harvey V. Fineberg is president of the Institute of Medicine.

The **National Research Council** was organized by the National Academy of Sciences in 1916 to associate the broad community of science and technology with the Academy's purposes of furthering knowledge and advising the federal government. Functioning in accordance with general policies determined by the Academy, the Council has become the principal operating agency of both the National Academy of Sciences and the National Academy of Engineering in providing services to the government, the public, and the scientific and engineering communities. The Council is administered jointly by both Academies and the Institute of Medicine. Dr. Ralph J. Cicerone and Dr. Wm. A. Wulf are chair and vice chair, respectively, of the National Research Council.

www.national-academies.org

COMMITTEE ON POSTMARKET SURVEILLANCE OF PEDIATRIC MEDICAL DEVICES

HUGH TILSON (*Chair*), Clinical Professor, Public Health Leadership, and Adjunct Professor of Epidemiology and Health Policy, University of North Carolina at Chapel Hill School of Public Health
JAMES M. ANDERSON, Professor of Pathology, Macromolecular Science and Biomedical Engineering, Institute of Pathology, Case Western Reserve University
ERLE H. AUSTIN III, Professor of Surgery, University of Louisville School of Medicine, and Chief, Cardiovascular Surgery, Kosair Children's Hospital
MARK E. BRULEY, Vice President, Accident and Forensic Investigation, ECRI
PAUL CITRON, Vice President (retired), Technology Policy and Academic Relations, Medtronic, Inc.
WILLIAM H. DUMOUCHEL, Vice President of Research and Chief Statistical Scientist, Lincoln Technologies, Inc.
ELLEN J. FLANNERY, Partner, Covington & Burling
LINDA GOLODNER, President, National Consumers League
STEPHEN J. HAINES, Lyle A. French Chair, Department of Neurosurgery, University of Minnesota Medical School
PATRICIA HICKS, Associate Professor of Pediatrics, University of Texas Southwestern Medical School
STEPHEN W. LAGAKOS, Chair, Harvard University School of Public Health, Department of Biostatistics
GEORGE LISTER, Professor and Chair, Department of Pediatrics, University of Texas Southwestern Medical School
JONATHAN J. ROSEN, Director, Office of Technology Implementation, Center for the Integration of Medicine and Innovative Technology

Committee Consultants and Background Paper Authors

JEFFREY P. BLOUNT, Assistant Professor of Surgery, Division of Pediatric Neurosurgery, University of Alabama at Birmingham
MARTIN J. BURTON, Consultant Otolaryngologist, Radcliffe Infirmary, Oxford University
DAVID FEIGAL, Research Professor, The Biodesign Institute at Arizona State University
ANNETINE C. GELIJNS, Co-Director, International Center for Health Outcomes and Innovation Research, Columbia University

BRIGID KILLELEA, Fellow, International Center for Health Outcomes and Innovation Research, Columbia University
JANICE M. LEUNG, Medical Student, Johns Hopkins University
VIPUL MANKAD, Professor of Medicine, University of Kentucky College of Medicine
ERIC A. MANN, Acting Deputy Director, General Surgery Device Branch, Center for Devices and Radiological Health
ALAN MOSKOWITZ, Co-Director, International Center for Health Outcomes and Innovation Research, Columbia University
JOHN K. NIPARKO, Professor, Otolaryngology-Head and Neck Surgery, Johns Hopkins University
DEBARA L. TUCCI, Associate Professor, Department of Surgery, Duke University
MICHAEL VITALE, Director, Pediatric Outcomes, International Center for Health Outcomes and Innovation Research, Columbia University

Study Staff

MARILYN J. FIELD, Study Director
MARGARET A. MCCOY, Research Associate
PERRY LUKSIN, Senior Project Assistant (until August 2004)
AYANNA N. VEST, Senior Project Assistant (from August 2004)

Board on Health Sciences Policy Staff

ANDREW POPE, Director, Board on Health Sciences Policy
AMY HAAS, Administrative Assistant

Preface

We hope that this report will put a face on the children who benefit every day from medical devices, lend a voice to some of the challenges they face in realizing the benefits of the devices, and give heart to those who want to make things even better. In spirit, our report is for these children and their families.

As written, this report responds to a request from Congress to investigate the questions described in the Summary and Chapter 1, and we have aimed much of our analysis and recommendations at legislative and administrative policymakers and those who advise them. At the same time, we have also tried to speak to the concerns of the broader community, including consumer and patient advocacy groups, concerned with the safe use of medical devices and the well-being of our nation's children.

Our committee profited greatly from face-to-face and other conversations with children; their parents and caregivers; the physicians, nurses, and other providers who take care of them and work diligently to assure safe use of devices; the scientists, engineers, and administrators who have attempted to understand and enhance the science of safety surveillance in the postmarket environment; the manufacturers who occupy such a vital place in the system of postmarket safety; and of course the regulators working to assure pre- and postmarket protections against problems with some medical devices. All provided valuable insights into the strengths and limitations of the enterprise and the opportunities to render it stronger. These, coupled with review of U.S. Food and Drug Administration (FDA) documents, clinical studies, and other secondary sources, sustained us in deep and far-reaching consideration and added reality and timeliness. We have drawn heavily on patient reports and clinical knowledge to illustrate child

and family experiences with medical devices in a series of vignettes (particularly in Chapter 4) that we hope will portray the benefits and the harms—actual and potential—that real children and families face every day.

As you read the results of our deliberations, we also hope that you will recognize—as we have—the following lessons.

First, children are not just "little adults." The biology and active lifestyles of children are unique and require particular attention during the development of medical products and procedures and also as part of continued monitoring and scientific assessment following their entry into clinical practice. And of course, the expected future life of the child undergoing therapy makes consideration of the multi-decade impact of medical interventions vital.

Second, medical devices are not just "mechanical drugs." Devices constitute a vital part of our therapeutic armamentarium, deserving no less attention than drugs and biologics and therapeutic nutritional products, but meriting recognition as a unique set of entities and challenges. The number and diversity of devices are remarkable, from the low-tech hospital bedrail and pervasive plastic tubing to the complex cardiac pacemaker and infant respirator. No simple approach to monitoring device safety in post-approval use will serve all situations.

Third, regulation of medical devices has required more than just "another sentence" in the FDA statutes regulating pharmaceuticals. Much of the devices industry is extremely fast-moving; many products have short half-lives, and continuous device improvement may be the rule, with new and improved replacements introduced rapidly into the marketplace. These features require a tailored regulatory approach that encourages innovation while protecting patients. And yet, when devices are approved with the potential for causing important harms, short term or with longer latency, this balance must consider effective means for long-term, population-based monitoring.

Fourth, monitoring the safety of devices cannot flourish as just a subfield of pharmacoepidemiology. Unique analytic approaches are needed for the unique characteristics of device use and outcomes. Many devices used in daily therapy are not identified by brand or batch number even to the institution, much less the end user. Furthermore, problems may arise far from the original place or time a device was used or implanted, for example, in the home or under the care of a physician not associated directly with the device, even in the case of implants. Added to the complexities of device research are the technical complexities of conducting pediatric studies, complexities that include small populations (which also may mean a small or nonexistent return on device development) and special research protection regulations.

Still, the committee finds much in the world of pharmaceuticals, in the experience of adults, in the regulation of drugs and biologics, and in the field of pharmacoepidemiology that can contribute to identification of inad-

equacies in protections related to pediatric medical devices and instruct in possible remedies. We can and must learn from these arenas.

Our explorations made it clear that the effort to protect the public's health in this area represents another example of the way public health systems in America function, as the collection of our society's efforts to assure conditions in which people, particularly children, can be healthy. Such systems entail many participants—public and private—often working in parallel but still unaware that they are part of a larger system of protections. Such incomplete connections among the components of the system or failure to approach things in a systematic way can lead to inefficient, even ineffective approaches in public health, including this sector. Thus, in order to assure adequate protections for children who rely on medical devices, we present recommendations that recognize and address the essential roles and responsibilities of the whole spectrum of actors in the system, from the regulator and manufacturer to the clinician and researcher, from officials in Washington, D.C., to patients and their families in homes across the country.

Some of our recommendations will be relatively easy to act on. Several of the professional societies we heard from, for example, are prepared to implement broader training on detection and reporting of device safety problems right now. Other recommendations will take more work. Better structured approaches to assure long-term monitoring of devices in children with potential for serious problems in the postmarket environment—without overburdening an often fragile industry—will take careful management, but we feel it must be done. Finding mechanisms to allow the evolving world of medical informatics to capture data about devices and link it automatically to other medical experience at the population level, for example, will take concerted efforts across multiple sectors of the health care system. We believe that all of our recommendations are feasible and necessary to assure adequate protections of our children in need of the benefits of medical devices.

We would like to thank those who took the time and trouble to tell us their stories and communicate their experiences as well as the many who provided important scientific, clinical, and analytic perspectives and evidence. As chair, I had the privilege of convening a knowledgeable and thoughtful committee, the members of which were willing to listen, learn, and, despite their varied backgrounds and sometimes quite disparate views, come together around the findings and recommendations which we present. Finally, let me thank our outstanding Institute of Medicine staff, particularly Marilyn Field, the project director, for her steady hand, quick mind, and great good sense.

Hugh Tilson, M.D., Dr.P.H.
Committee Chair

Acknowledgments

The committee and staff are indebted to a number of individuals and groups for their assistance in the development of this report. The committee learned much through workshops and public meetings it organized to obtain information and perspectives from groups and individuals knowledgeable and concerned about research involving infants, children, and adolescents. Appendix A includes the meeting agendas and participant lists and cites the organizations that did not participate in the meeting but provided written statements to the committee.

Special thanks go to the family members who talked with us by telephone and met with us to share their experiences of living day-to-day with complex, life-sustaining devices. They enriched our understanding of the varied benefits and stresses of child and family life with complex medical devices. We also appreciate the contributions of the outside authors of the background papers presented as appendixes to this report, particularly John Niparko and Janice Leung (Johns Hopkins University), Jeffrey Blount (University of Alabama at Birmingham), and Annetine Gelijns and Alan Moskowitz (Columbia University).

A number of people at the Food and Drug Administration (FDA) provided important background and information for this study. Thomas Gross, the agency's project officer for the study, was unfailingly helpful. He directly answered many questions about the agency's postmarket surveillance program and related activities and also sought the expertise of his colleagues on other questions about aspects of the agency's work. Susan Gardner, Roselie Bright, Donna-Bea Tillman, Joanne Less, Lori Brown, Deborah Yoder, and

Gregory Campbell are among those who provided additional understanding of FDA's policies and programs.

We appreciate the opportunity provided by the American Academy of Pediatrics, the National Organization for Rare Disorders, and the Elizabeth Glazer Pediatric AIDS Foundation to participate in meetings on barriers to the development of devices for pediatric use. The discussions provided insights that are relevant throughout the medical device development cycle. Elaine Vining (American Academy of Pediatricians) and Jeanne Ireland (Elizabeth Glazer Pediatric AIDS Foundation) also offered additional ideas and information. Jon Abramson (Wake Forest University), who led these meetings, described his discussions with the FDA some years ago to discuss surveillance of pediatric medical devices, among other topics.

Among many who helped the committee clarify issues, find important information, or otherwise complete its work are Robert Campbell (University of Texas Health Sciences Center, San Antonio); Jennita Reefhuis (Centers for Disease Control and Prevention); Sonja McKinley and Lynn Sleeper (New England Research Institute); Robert Bartlett (University of Michigan); Anthony Slonim, Billie Short, and K. Rais-Bahrami (Children's National Medical Center); Richard Platt (Harvard University); Andrew Mahar (Childen's Hospital San Diego); Frank Johnson (St. Louis University); Tara Federici (AdvaMed); Susan Alpert and Laura Visser (Medtronic); Hope Treviso (Thoracic Institute); Kit Song and Kristie Bjornson (University of Washington); Cliff Megerian (Case Western University); Barry Rumack; James Donahue (Marshfield Clinic Research Foundation); Alexander Walker (Ingenix); Adam Feuerstein (TheStreet.com); Sue Tolleson-Rinehart, Alan Stiles, Ali S. Calikoglu, and colleagues at the University of North Carolina; Richard Platt (Harvard Medical School); James Donahue (Marshfield Clinic Research Foundation); Richard Chinook (Loma Linda University); Alex Walker (Ingenix); Steven Webber (University of Pittsburgh).

As usual, many within the Institute of Medicine were helpful to the study staff. The committee would especially like to thank William McLeod, Sally Stanfield, Michele de la Menardiere, James Hinchman, Julie Wiltshire, Janice Mehler, Alex Ommaya, Marie Michnich, Clyde Behney, and Jennifer Bitticks.

Reviewers

This report has been reviewed in draft form by individuals chosen for their diverse perspectives and technical expertise, in accordance with procedures approved by the National Research Council's Report Review Committee. The purpose of this independent review is to provide candid and critical comments that will assist the institution in making its published reports as sound as possible and to ensure that the report meets institutional standards for objectivity, evidence, and responsiveness to the study charge. The review comments and draft manuscript remain confidential to protect the integrity of the deliberative process. We wish to thank the following individuals for their review of this report:

Edward M. Basile, J.D., King & Spalding, L.L.P.
Bruce Boissonnault, Niagara Health Quality Coalition
Francis Sessions Cole, III, M.D., Washington University in St. Louis
Neal E. Fearnot, Ph.D., MED Institute, Inc., Cook Group Incorporated
Harry A. Guess, M.D., Ph.D., University of North Carolina at Chapel Hill
Jonathan S. Kahan, J.D., Hogan & Hartson, L.L.P.
Elizabeth Magill, J.D., University of Virginia Law School
Cliff A. Megerian, M.D., Case Western Reserve University
Michael R. Neuman, Ph.D., M.D., Michigan Technological University
Robert J. Panzer, M.D., University of Rochester Medical Center
Frederick J. Schoen, M.D., Ph.D., Harvard Medical School
Deborah Shatin, Ph.D., Center for Health Care Policy and Evaluation
Anthony D. Slonim, M.D., M.P.H., Children's National Medical Center
Michael G. Vitale, M.D., M.P.H., International Center for Health Outcomes and Innovation Research
John Thomas Watson, Ph.D., Jacobs School of Engineering Von Liebig Center

Although the reviewers listed above have provided many constructive comments and suggestions, they were not asked to endorse the conclusions or recommendations nor did they see the final draft of the report before its release. The review of this report was overseen by **RICHARD B. JOHNSTON, JR., M.D.,** University of Colorado School of Medicine and **EDWARD B. PERRIN, Ph.D.,** University of Washington. Appointed by the National Research Council and the Institute of Medicine, these individuals were responsible for making certain that an independent examination of this report was carried out in accordance with the institutional procedures and that all review comments were carefully considered. Responsibility for the final content of this report rests entirely with the authoring committee and the institution.

Contents

Boxes, Figures, and Tables

BOXES

FIGURES

TABLES

Summary

Advances in biomedical science and engineering—combined with achievements in public health—have brought significant benefits to millions of children and their families. Vaccines and drugs are often cited, but medical devices too have helped reduce the burden of illness and injury and improve the quality of life for countless children. For example, mechanical ventilators, in combination with medications and additional therapies, rescue thousands of fragile newborns each year and allow many children who rely on respiratory support to live at home with their families, attend school, and participate in community life. Children who once would have died from congenital heart conditions today survive with the aid of implanted devices such as pacemakers, mechanical heart valves, and devices that close holes in the heart. In addition, a multitude of simple devices such as catheters and other kinds of tubing are essential for modern medical care.

As depicted in Box S.1, some medical devices are intended solely or primarily for use with children. Often, however, devices used with children have been initially developed for, tested with, and most frequently employed to treat adults, who constitute a much larger market for medical services than children.

Sometimes it is obvious that a device developed for adults is not—in that form—suitable for some children, for example, when an implanted device is too large for infants. Other times, problems with pediatric use—such as more intense inflammatory reactions to implant materials than seen with adults—are not self-evident and are also not detected during initial clinical studies. Instead, problems are only identified after a device is mar-

BOX S.1
Design or Adaptation of Medical Devices for Use with Children

Devices unique to children
- Infant incubators
- Bililights (for treating neonatal jaundice)
- Newborn hearing screener

Devices developed primarily for children but also used with adults
- Atrial septal defect occluder
- Cerebrospinal fluid shunt

Same core device, different accessories for pediatric use
- Pulse oximeter with different sensor attachment for infants
- Automated external defibrillator with paddles that deliver electrical shocks based on pediatric-specific algorithms

Variations in device use or technique to accommodate developmental differences
- Adjustment in radiation dose and frequency for computed tomography
- Shift in implantation site for pacemakers used with young children
- Use in pediatric cardiac procedures of adult bile duct stents

Variation in device size for use with small patients
- Bronchoscopes
- Heart valves
- Testicular prostheses

keted and then used for longer periods and with larger and more varied populations, including children.

As illustrated in Box S.2, benefits and harms with pediatric use of medical devices may be identified in several ways: (1) *a priori* based on expert understanding of children's developmental characteristics and detailed knowledge and modeling of the operating characteristics of a particular device; (2) during the clinical testing of a device with children to demonstrate safety and effectiveness; and (3) as experience with a device accumulates following its entry into the market. At each stage, the key questions are whether the expected benefits of a device, on balance, outweigh expected harms and whether the benefit–harm profile is more favorable than that of available alternatives.

STATEMENT OF TASK

This report responds to a provision in the Medical Device User Fee and Modernization Act of 2002 (P.L. 107–250) that called for the Institute of Medicine (IOM) to assess whether "the system under the Federal Food, Drug, and Cosmetic Act for the postmarket surveillance of medical devices

BOX S.2
Identifying Concerns or Adaptations with Pediatric Use of Medical Devices (with Examples)

A priori identification
- Pacemaker implant: choice of implant site to better protect device
- Deep brain stimulator: avoidance of use when patient brain growth is less than 90 percent complete
- Orthopedic fixation device: avoidance of device that will interfere with bone growth

Identification through premarket clinical testing
- Deep brain stimulator: modification of implant placement when two stimulators are used with small child
- Titanium rib: modification of device and implantation strategy to reduce migration or bone overgrowth

Identification after marketing
- Cochlear implant: association of meningitis with certain devices
- Home apnea monitors: lack of effectiveness in detecting apnea consistently and preventing sudden infant death syndrome

provides adequate safeguards regarding the use of devices in pediatric populations." The IOM was to examine specifically: (1) the U.S. Food and Drug Administration's (FDA) monitoring and use of adverse reaction reports, registries, clinical studies, and other postmarket surveillance activities; (2) the adequacy of FDA's monitoring of commitments for further clinical studies made by manufacturers at the time of approval of specific devices; (3) the adequacy of postmarket surveillance studies to evaluate how children's active lifestyles may affect failure rates and longevity for implanted devices; and (4) the length of postmarket surveillance studies of implanted devices, including whether studies continue long enough to evaluate the impact of children's growth and development given the expected length of time that a child will have an implant. The committee was not asked to evaluate FDA's premarket review of medical devices or to assess barriers to the development of medical devices to meet children's special needs.

Postmarket surveillance of medical devices used with children is a little-investigated topic. This is partly because the market for most medical products is concentrated among adults, especially older adults. Moreover, discussions of medical product regulation and patient safety focus more on pharmaceuticals than on medical devices and more on the assessment of products prior to marketing than on the subsequent surveillance of product performance.

During the course of this study, several themes emerged. They include:

- *Children and their families benefit from safe, effective medical devices.* Timely access to such devices prevents premature deaths and significantly improves quality of life.
- *Systematic attention to children's needs and characteristics is important in medical device design, use, and evaluation.* Children differ from adults in important ways.
- *An effective regulatory program for evaluating and monitoring the safety of medical devices in general is a necessary foundation for efforts to safeguard children in particular.* This basic foundation then requires the addition of pediatric expertise and resources.
- *The regulation of medical devices reasonably differs from the regulation of drugs.* Medical devices are more variable than drugs in their mode of operation, range of function, dependence on user skills, and potential for harm.
- *A careful assessment of medical device regulations weighs potential positive and negative outcomes, including whether the potential negative effects of a regulation are acceptable.* Like medical treatments, regulations can do harm as well as good.
- *The shift of medical device use from institutions to homes, schools, and the community complicates postmarket surveillance.* Patients, families, and others have taken on roles in device operation, maintenance, and troubleshooting that were formerly performed by health care professionals, but postmarket surveillance has not yet adapted to this reality.
- *Medical device safety is a shared responsibility.* Clinicians, health care providers, engineers, manufacturers, research funding agencies, consumer organizations, patients and families, and others in addition to regulators have critical roles to play.

FDA REGULATION, MEDICAL DEVICES, AND CHILDREN

Medical devices constitute an extremely varied category of medical products—some as simple and low risk as an infant cap, others as complex and high risk as a cardiac pacemaker. Unlike drugs, which work chemically, devices such as pacemakers, artificial joints, ultrasound machines, and mechanical ventilators have quite different and variable modes of operation. The statutes governing the regulation of medical devices by FDA reflect this variability, particularly in provisions specifying the agency's premarket responsibilities, that is, what it does before a device can be legally marketed.[1]

[1]In referring to *premarket* and *postmarket* rather than *premarketing* and *postmarketing* activities, this report follows the legislative language that provided for this study and FDA's usual terminology.

In simplified overview, low-risk devices need not be reviewed by FDA before marketing. Innovative, high-risk devices are subject to an *approval* process that evaluates clinical and other studies of safety and effectiveness. Intermediate-risk devices go through a *clearance* process that involves a more limited review of evidence of safety and equivalence to certain previously marketed devices; clinical evidence of safety and effectiveness is not usually required. Additional regulations, particularly those intended to assure quality and safety in manufacturing, apply to all devices.

After devices enter the market, FDA's postmarket surveillance includes requirements or opportunities for manufacturers, health care facilities, and others to report serious problems—adverse events—that are caused or potentially caused by any kind of medical device or errors in its use. For certain devices, the agency can also require postmarket studies to evaluate device performance or safety as devices are used for longer periods, in different settings, and with more varied patients than during their initial testing. FDA's public health notifications, monitoring of device recalls, and inspections of device manufacturing sites are additional postmarket tools to assure the safety of medical devices.

Virtually the entire regulatory framework for the regulation of medical devices is general; that is, it applies to devices whether their primary or exclusive use is with adults or children. One exception is that when devices are tested with children in studies that will be submitted to FDA, the studies are covered by regulations for the protection of human research subjects that provide additional protections for children. Also, FDA may take special notice of children, for example, by limiting the approved use of a device to patients over a specific age.

FDA PERFORMANCE IN BRIEF

The basic goal of FDA's program of postmarket surveillance for medical devices is to protect patients from harm by identifying and evaluating safety problems and assuring appropriate corrective responses, such as a recall or a precautionary notice to physicians. As undertaken by FDA, postmarket surveillance should be seen as objective, trustworthy, and effective in limiting patient exposure to unsafe devices (or to devices unsafely used). It should seek to minimize avoidable constraints on beneficial innovation while also serving as a resource and stimulus for product improvement.

With respect to the questions posed for the IOM, this report notes some shortfalls in FDA performance. These shortfalls, by and large, are not specific to children, so responses must be general. Although evaluating FDA resources for postmarket device surveillance was beyond the scope of this study, the committee notes that Congress has authorized but not appropriated additional funds for such surveillance.

The discussion below highlights selected recommendations (which are numbered by report chapter). All recommendations are listed at the end of the summary.

Monitoring of Postmarket Study Commitments

The most obvious deficits in FDA's performance are the agency's lack of effective procedures for monitoring the status of required postmarket studies and the lack of public information regarding such studies. One consequence for this report was that neither the agency nor the committee could reliably identify required postmarket studies that included questions related to children's growth and development or active lifestyles.

The agency recently announced plans to shift responsibility for study monitoring within the Center for Devices and Radiological Health (CDRH) to the postmarket surveillance unit. It has not released details, including what information will be made public.

Recommendation 5.1: Congress should require FDA to establish a system for monitoring and publicly reporting the status of postmarket study commitments involving medical devices. The system should also cover voluntary studies negotiated between FDA and manufacturers as part of the device approval or clearance process. The public database should, among other features, allow easy determination of the status of postmarket studies that involve questions about device use with children.

Public Access to Information About Postmarket Studies

Monitoring of postmarket study commitments is important but so is greater openness about study methods and findings. Given the limited research on medical devices used with children, FDA should, at a minimum, provide for more open access to information about required pediatric studies. The details (e.g., how to screen studies for soundness before making results public) will require careful consideration so that the agency does not publicize findings from studies that are badly designed, poorly executed, or inappropriately analyzed. Continuing discussions about the design of a public clinical trials registry may yield useful guidance.

Recommendation 5.2: FDA's system for monitoring and reporting postmarket study commitments should include information about the disposition of study findings, for example, a change in the labeling of a device. It should also provide for the responsible and understandable reporting of the source, methods, and findings of monitored postmarket studies.

Adequacy of Required Postmarket Studies

Without a systematic database of postmarket device studies, FDA could not identify for the committee those studies that involved children or investigated growth and development, activity levels, or other pediatric questions. Furthermore, because statutes on trade secrets and confidentiality require FDA to hold study protocols and much other information confidential, even if the committee knew of a relevant pediatric study, it might not have been able to learn enough about the study to assess it.

FDA's authority to order postmarket studies is limited. It cannot require studies as a condition of clearing devices for which the more extensive premarket approval process is not required. In addition, for devices that have already been approved or cleared, the agency cannot require studies to last more than 3 years. For children, some important developmental consequences may not be evident within that period.

Recommendation 6.5: Congress should amend Section 522 of the Federal Food, Drug, and Cosmetic Act to

- permit FDA to order postmarket studies as a condition of clearance for the categories of devices for which Section 522 Postmarket Surveillance studies are now allowed and
- allow FDA to tailor the duration of Section 522 studies of devices likely to have significant pediatric use so that studies can take into account children's growth and development and, if appropriate, exceed the current 3-year limit on study length.

The committee recognizes that most postmarket research does not result from FDA requirements but is undertaken voluntarily by industry, academic, and other researchers. The committee also recognizes that a requirement for a postmarket pediatric study might, in some cases, prompt a device manufacturer to label a device as not indicated for use with children rather than incur the costs of a study. Thus, FDA should promote additional strategies for building new knowledge that extend beyond required manufacturer studies.

Recommendation 6.6: FDA should collaborate with the National Institutes of Health, the Agency for Healthcare Research and Quality, and other research funding agencies and interested parties to define a research agenda and priorities for the evaluation of the short- and long-term safety and effectiveness of medical devices used with growing and developing children.

The expanding use of electronic patient information systems presents opportunities to strengthen studies of device outcomes and also improve surveil-

lance for adverse events. Capitalizing on these opportunities will require further work to develop feasible coding standards that allow more precise identification of specific types and models of devices than is possible now.

Recommendation 6.2: As part of government and private health informatics initiatives, such as those supporting the electronic medical record, FDA should promote the development and adoption of common device coding and other standards and approaches for capturing and linking use and outcomes data for medical devices. FDA should also work with agencies such as the Agency for Healthcare Research and Quality and university- and industry-based methodologists to strengthen methods and tools for epidemiologic research on medical device safety.

Adverse Event Reporting

Judgments about the adequacy of FDA's program of adverse event reporting must take into account the generally recognized problems with such reporting. Underreporting and incomplete or inaccurate reporting are not confined to this program.

In important respects, substantial progress in detecting, reporting, understanding, and preventing adverse device events will depend less on FDA regulations than on the collective results of institutional and collaborative efforts by health care institutions, professional societies, state and federal public health agencies, and others. FDA is, however, uniquely situated to promote attention to events related to medical devices.

Recommendation 4.1: FDA should collaborate with industry, health care professionals and organizations, and parent and patient advocates to

- focus more attention on adverse device events, including events involving children;
- promote linkages between adverse event reporting systems, various FDA databases, and other safety programs;
- update product labeling, patient information, and other communications to promptly reflect safety-related findings from analyses of adverse event reports; and
- issue yearly reports on results from adverse event analyses, including findings involving children.

The evaluation plan for the MedSun program (the agency's pilot Medical Product Surveillance Network, which involves more intensive and active interaction with a sample of 300 medical facilities, including more than 20 children's hospitals) should, among other elements, include comparisons of

adverse event reports from MedSun and the mandatory user facility reporting system. It should assess the extent to which either program produced important reports that were missed or delayed by the other (Recommendation 4.3).

With MedSun, the agency has an opportunity to use the participating children's hospitals as connecting points to strengthen device-related surveillance at other hospitals serving children. Adverse event reporting is particularly important for medical devices in pediatric use because pediatric events are often unusual and sometimes extreme, and involve problems in a patient population that frequently has not been studied before marketing.

Recommendation 4.7: Children's hospitals and other user facilities should establish a focal point of responsibility for medical device safety. Tasks include reviewing and monitoring the adequacy of institutional programs in areas such as tracking of safety alerts and recalls, responding to safety alerts and recalls, training in adverse event evaluation and reporting, and factoring safety data or evaluations into device purchase decisions.

Independent Oversight

In February 2005, the Department of Health and Human Services (DHHS) announced the creation of an independent drug safety oversight board within FDA (but outside the Center for Drug Evaluation and Research) to oversee the management of high-profile drug safety issues. The board would also provide "emerging information" to clinicians and patients about the risks and benefits of medicines. That is, discussion of potential safety problems would not wait until FDA reached firm enough conclusions to prompt a safety alert or other action. The board would include experts from FDA and elsewhere in DHHS and other government departments.

Notwithstanding certain differences between drugs and devices, the criteria for responsibly making emerging drug safety information public and overseeing high-profile issues should—if soundly designed and implemented—apply, at least in broad outline, to the evaluation of similar information from postmarket studies of medical devices. Whether the independent board approach is advisable for medical devices is another matter. In particular, whether such a board could obtain sufficient independent technical and clinical expertise would need careful assessment.

Organizational Attention to Pediatric Issues

In addition to calling for this study, Congress has directed attention to pediatric device safety in other ways, for example, by directing FDA to

prepare reports on premarket assessment of pediatric medical devices, barriers to pediatric device development, and pediatric expertise for device safety advisory panels. Also as directed by Congress, FDA created an Office of Pediatric Therapeutics to coordinate and facilitate FDA activities that affect children and the practice of pediatrics, but its activities focus almost entirely on drugs.

Recommendation 7.1: FDA should establish a central point of responsibility for pediatric issues within the Center for Devices and Radiological Health to evaluate the adequacy of the Center's use of pediatric expertise and its attention to pediatric issues in all aspects of its work.

TENSIONS IN PUBLIC POLICY AND DEVICE INNOVATION

FDA is charged with simultaneously safeguarding public safety and encouraging timely access by patients to beneficial new products. Recent controversies have focused attention on tensions between these two broad roles. Tension may also exist between the public's desire for government to protect them from an array of threats to their health and safety and their willingness to pay for such protection.

Another area of tension centers around trade secret and confidentiality provisions related to studies of FDA-regulated products. In this case, the objective of encouraging product innovation by allowing innovators to hold certain information secret can sometimes conflict with the objective of providing clinicians and patients with full information to guide decisions. Special regulatory protections for children involved in research may also impede certain kinds of research.

SHARED RESPONSIBILITIES FOR MEDICAL DEVICE SAFETY

Medical device safety is a shared responsibility that necessarily involves manufacturers, researchers, clinicians, engineers, health care facilities, regulators, and patients and families. The sharing of responsibilities extends throughout the medical device product cycle—from innovation and development through testing, marketing, clinical use, safety monitoring, and eventual refinement or replacement.

This spectrum of shared responsibility for device safety itself operates within a broader system of shared responsibilities for overall patient safety and health care quality. In the past two decades, institutional and collaborative initiatives to improve the quality of health care and protect patients from harm have grown to involve a wide range of public and private parties. This diversity of involvement reflects not only the broad concern about health care quality and patient safety but

also the range of parties whose participation is essential to improve health outcomes.

Patient safety initiatives often emphasize drug safety. The focus on medications reflects analyses of medical errors in which medication mishaps figure prominently, although some of these mishaps also involve flaws in device design or use. Like most patient safety initiatives, initiatives that focus on children tend not to feature medical devices.

Still, even programs that focus on adults, drug safety, or other topics may encourage practices, procedures, and ways of thinking that can—indirectly or directly—help create an environment that promotes the safe use and design of medical devices for children. For example, increased expertise in root cause analysis of medical errors and assessment of human factors can be broadly applied. Beyond appreciating such spillover effects, those concerned about device safety can consider how quality of care and safety initiatives might be expanded or adjusted to include medical devices.

Recommendation 7.2: All those engaged in improving the quality of health care and protecting patients from harm should evaluate and sharpen as appropriate their attention to medical device safety, including safety issues that particularly affect children.

Complete List of Recommendations

Adverse Event Reporting

Recommendation 4.1: FDA should collaborate with industry, health care professionals and organizations, and parent and patient advocates to

- focus more attention on adverse device events, including events involving children;
- promote linkages between adverse event reporting systems, various FDA databases, and other safety programs;
- update product labeling, patient information, and other communications to promptly reflect safety-related findings from analyses of adverse event reports; and
- issue yearly reports on results from adverse event analyses, including findings involving children.

Recommendation 4.2: FDA should continue educational and communication programs to promote recognition and useful reporting of serious adverse device events and device problems by hospitals and other user facilities. Such encouragement should continue whether or not requirements for mandatory reporting by user facilities are eventually eliminated with the

effective implementation of the MedSun program. Reporting by user facilities of events possibly related to devices should continue to include deaths, serious injuries, and device malfunctions.

Recommendation 4.3: FDA's plan for evaluating MedSun's performance as a replacement for and improvement on mandatory user facility reporting should include, among other elements,

- assessment of ongoing program and participant facility success in educating facility personnel about identifying, evaluating, and reporting adverse device events and improving the quality, timeliness, and usefulness of event reports;
- determination of the extent to which the sample of MedSun participating hospitals—including children's hospitals—represents the relevant range of facility characteristics and experiences, including representation of both academic medical centers and community hospitals and sufficient representation of facilities with device-oriented specialties and procedures;
- comparison with the mandatory user facility reporting system, including the extent to which either program produced reports for FDA or manufacturers of emerging hazards, important close calls, or other significant events (including those involving children) that were missed or delayed by the other; and
- evaluation of the active surveillance components of the program in reducing harm to patients, promoting constructive communication between facilities and FDA, and improving timely knowledge of the nature and extent of selected device problems, including errors in the use and design of devices.

Recommendation 4.4: Within the pilot MedSun program, FDA and participating children's hospitals should serve as a resource for the broader involvement of children's hospitals in patient safety programs to identify, evaluate, respond to, or prevent problems with the use and design of medical devices. In addition, FDA should promote efforts to link or otherwise employ event reporting, device recall, safety notification, and other databases within and outside FDA to better assess and report on device safety issues involving children.

Recommendation 4.5: When FDA mandates or agrees to device labeling that requires professionals to be trained in the safe and appropriate use of a medical device, the training should include information on the identification of adverse events, voluntary adverse event reporting under MedWatch,

and user facility and manufacturer medical device reporting (MDR) requirements.

Recommendation 4.6: Medical, surgical, and other organizations or societies that include health professionals who care for children should

- establish working groups to evaluate problems as well as benefits in the pediatric use of devices of particular importance to their practice;
- collaborate with existing public and private patient safety initiatives to add or expand attention to safe and appropriate use of medical devices with children;
- establish standards for professional education and competency in the use of these devices; and
- include as professional competencies the identification and appropriate reporting of device problems and the successful communication with patients and families about how to prevent, recognize, and respond to device problems.

Recommendation 4.7: Children's hospitals and other user facilities should establish a focal point of responsibility for medical device safety. Tasks include reviewing and monitoring the adequacy of institutional programs in areas such as tracking of safety alerts and recalls, responding to safety alerts and recalls, training in adverse event evaluation and reporting, and factoring safety data or evaluations into device purchase decisions.

Recommendation 4.8: FDA should continue to improve and expand its medical device safety resources for patients and families and its focus on devices used in the home and community by

- working with patient, family, and consumer organizations, providers, and industry to make it easier for patients or their families to report device problems to manufacturers or FDA and to learn about resources to support the safe use of medical devices;
- making online reporting and information resources more accessible by using language and directions appropriate for lay users; and
- enlisting hospitals, home care agencies and vendors, and other professional and provider groups to promote patient and family understanding of how to use devices safely, when and how to seek help, and when and how to report problems.

Monitoring Study Commitments

Recommendation 5.1: Congress should require FDA to establish a system for monitoring and publicly reporting the status of postmarket study com-

mitments involving medical devices. The system should also cover voluntary studies negotiated between FDA and manufacturers as part of the device approval or clearance process. The public database should, among other features, allow easy determination of the status of postmarket studies that involve questions about device use with children.

Recommendation 5.2: FDA's system for monitoring and reporting postmarket study commitments should include information about the disposition of study findings, for example, a change in the labeling of a device. It should also provide for the responsible and understandable reporting of the source, methods, and findings of monitored postmarket studies.

Strengthening Postmarket Studies

Recommendation 6.1: FDA should develop additional guidance for its own staff as well as for manufacturers and investigators on the identification and evaluation of pediatric questions or concerns at all stages in the design and evaluation of medical devices used with children.

Recommendation 6.2: As part of government and private health informatics initiatives, such as those supporting the electronic medical record, FDA should promote the development and adoption of common device coding and other standards and approaches for capturing and linking use and outcomes data for medical devices. FDA should also work with agencies such as the Agency for Healthcare Research and Quality and university- and industry-based methodologists to strengthen methods and tools for epidemiologic research on medical device safety.

Recommendation 6.3: As a resource for itself and others, FDA should create or collaborate with others to create a registry of relevant registries, that is, a database with information about registries that are either device specific or that have the potential to provide information useful in evaluating device safety and effectiveness.

Recommendation 6.4: As part of a public commitment to postmarket surveillance of device safety, the Center for Devices and Radiological Health should have its own extramural research program to support studies using external data sources.

Recommendation 6.5: Congress should amend Section 522 of the Federal Food, Drug, and Cosmetic Act to

- permit FDA to order postmarket studies as a condition of clearance for the categories of devices for which Section 522 Postmarket Surveillance studies are now allowed and
- allow FDA to tailor the duration of Section 522 studies of devices likely to have significant pediatric use so that studies can take into account children's growth and development and, if appropriate, exceed the current 3-year limit on study length.

Recommendation 6.6: FDA should collaborate with the National Institutes of Health, the Agency for Healthcare Research and Quality, and other research funding agencies and interested parties to define a research agenda and priorities for the evaluation of the short- and long-term safety and effectiveness of medical devices used with growing and developing children.

Responsibilities for Medical Device Safety

Recommendation 7.1: FDA should establish a central point of responsibility for pediatric issues within the Center for Devices and Radiological Health to evaluate the adequacy of the Center's use of pediatric expertise and its attention to pediatric issues in all aspects of its work.

Recommendation 7.2: All those engaged in improving the quality of health care and protecting patients from harm should evaluate and sharpen as appropriate their attention to medical device safety, including safety issues that particularly affect children.

1

Introduction

In 1956, John and Mary Holter were shattered when their son, Casey, was born with spina bifida and hydrocephalus (water on the brain). Doctors told the Holters that the opening of the spine on their son's back could be repaired but that they had not yet found a successful way to manage the buildup of spinal fluid in Casey's brain, a process that would eventually kill him.

Mr. Holter, a self-described "mechanic" who worked in a lock company's research lab, decided to tackle the fluid problem. He developed a small, one-way valve that he thought would allow the brain fluid to drain and save his son's life. He prevailed upon the child's neurosurgeon, Eugene Spitz, to use the untested device, which was made of silicone, a new material. Casey lived an unexpected 5 years before dying from other causes.

The Holter valve made drainage or shunting of cerebrospinal fluid a practical reality. Today, after years of technical modification and adjustment in clinical procedures, about 30,000 shunt procedures are done in the United States each year. The life expectancy of children with hydrocephalus is now measured in decades, not years, and hydrocephalus is no longer the end of a family's dreams.

(Baru et al., 2001; Basse, 2003)

Through the determined creativity of single individuals such as John Holter and the contributions of organized teams of medical and engineering researchers, advances in biomedical science and engineering—combined with achievements in public health—have brought innumerable benefits to millions of children and their families and communities. Notably, in addition to improved sanitation and nutrition, the development of vaccines to prevent common childhood diseases and antibiotics to treat infections have saved the lives of countless children. Although medical devices such as syringes, intravenous infusion equipment, and infant-sized catheters have played supporting roles in immunizations and antibiotic therapy, devices have figured most prominently in other areas of pediatric health care.

For example, mechanical ventilators and other respiratory support devices in combination with medications and other therapies rescue thou-

sands of fragile newborns each year, including babies born prematurely with lungs that are insufficiently developed to sustain independent breathing. Some infants rely on these devices only briefly, but others with chronic health conditions use these life-sustaining devices for years. As shown below in the photographs of older and newer ventilatory support equipment (Figures 1.1 and 1.2), reductions in the size of equipment and other advances now allow many children who rely on these devices to live at home with their families, attend school, and participate in community life.

To cite another example, children who once would have died from congenital heart conditions today survive with the aid of implanted devices such as mechanical heart valves, pacemakers, devices that close holes in the heart, and artificial tubes used to bypass malformed heart valves. The surgical procedures associated with these and other treatments typically require additional sophisticated equipment, including cardiopulmonary bypass systems (heart–lung machines that oxygenate and circulate the blood while the heart is stopped for surgery), devices that provide anesthesia, and equipment that monitors breathing, oxygen levels, and other critical physiologic variables and warns clinicians of impending trouble. Box 1.1 lists examples of life-saving and life-sustaining devices that benefit children.

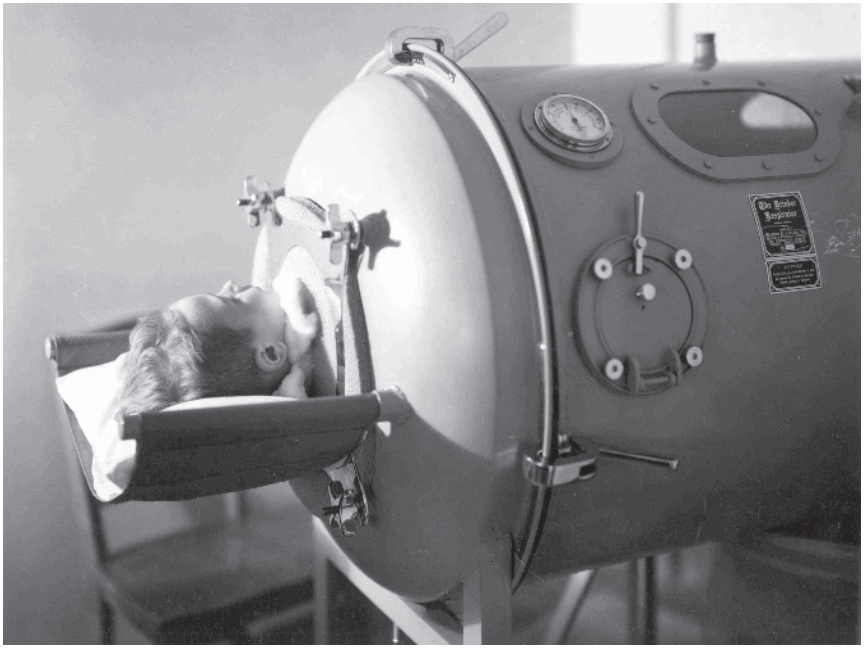


FIGURE 1.1 Child in iron lung, World Health Organization, c. 1938 (Used with permission of IUPUI University Library Special Collections and Archives).

FIGURE 1.2 Zoe and Dad on a hike (Courtesy of Lynne Andersson and Stephen Andersson).

This report examines the regulation and surveillance of a wide range of medical devices used with children. In some cases, these devices are intended solely or primarily for use with children. Examples include newborn incubators, inhaled nitric oxide delivery units for certain newborns with respiratory problems, and "bililights" or "biliblankets" that provide phototherapy for infants with jaundice. The design and evaluation of these devices will necessarily focus on the children expected to use the devices.

Some devices now widely used with adults were first aimed at pediatric conditions. For example, the first external pacemakers were developed for children who were born with cardiac anomalies that required surgical correction and subsequent pacing of the heart rhythm. Initially, the devices

BOX 1.1
Examples of Life-Saving and Life-Sustaining Medical Devices for Children

Mechanical ventilators: Negative-pressure ventilators or "iron lungs," which were developed in the late 1920s by Drinker and Shaw, supported children with respiratory failure from poliomyelitis into the 1950s. Subsequently, the positive-pressure ventilator became widely used to support virtually all infants and children in need of assisted breathing related to acute or chronic respiratory failure. Although it is difficult to attribute improved outcome to any single factor when many aspects of care have changed, the management of respiratory distress using mechanical ventilation in premature infants is one area where the increased survival is well documented (Gregory et al., 1971; Farrell and Avery, 1975).

Balloon atrial septostomy (Rashkind procedure): This nonsurgical, catheter-based procedure provides a way for oxygenated blood to get to the systemic tissues in infants with transposition of the aorta and the pulmonary artery (a congenital heart defect that starves the blood of oxygen). It stabilizes the newborn until definitive surgery can be performed. The development of the device and associated surgical techniques led to a dramatic increase in survival of affected infants. One-month survival rates rose from approximately 10 percent in the early 1960s to more than 90 percent after the procedure became widely used (Rashkind and Miller, 1968; Liebman et al., 1969; Rashkind et al., 1969; Rashkind, 1971, 1983).

Cerebrospinal fluid shunt for hydrocephalus: For infants and others suffering from inadequate draining of cerebrospinal fluid from the brain, the hydrocephalus shunt has reduced mortality from approximately 50 percent to approximately 10 percent (Gilmore, 1990; Staal et al., 1997). The device consists of a silicone tube that is passed through the brain into the cerebrospinal fluid-containing ventricles and connected under the scalp to a one-way valve. This valve drains through a longer silicone tube into the abdominal cavity, the veins that drain into the heart or, rarely, other body cavities. Modern valves can have their drainage pressure characteristics adjusted noninvasively after implantation. Although still plagued with problems of infection and blockage requiring surgical repair, cerebrospinal fluid shunts allow more than half of children with hydrocephalus to avoid brain damage and developmental delay caused by prolonged increased spinal fluid pressure on the brain (Casey et al., 1997).

Pulse oximetry: In years past, the standard technique for assessing the body's oxygenation was to obtain a sample of arterial blood by needle puncture or through an indwelling catheter. This presented many complications for small infants with conditions that left them at risk for a life-threatening lack of oxygen. It required removal of blood, which might ultimately necessitate a transfusion if there were multiple samples, and it could be technically difficult to obtain the sample from a small baby. The development of the pulse oximeter, a device that passes a light wave through an extremity (e.g., a finger or toe) to "see" the color of the blood in the capillaries and, hence, assess the amount of oxygen, was a tremendous advance. It could measure oxygenation continuously, which was particularly valuable during operations and in the care of critically ill infants.

plugged into wall sockets, which meant they severely limited the children's mobility during recovery and were fatally useless during a power interruption. Although simple by today's standards, the external battery-powered pacemaker was a revolutionary development, and it was soon followed by the implantable pacemaker. This innovation helped establish what is now a large and very successful medical electronics industry (see, e.g., Rhees and Jeffrey, 2000).

In many cases, medical devices used to help children have been initially developed for, tested with, and most frequently employed to treat adults, who constitute a much larger market for medical devices and medical treatments than children, who are, overall, a healthier segment of the population. As discussed further in Chapter 2, implants and other devices may require modification for use with infants and children to account for differences in overall body size as well as in the dimensions of body structures such as blood vessels. Furthermore, because children are not small adults, the design, use, or monitoring of certain devices may need to take into account not only size but also children's physical, cognitive, and emotional growth and development.

Sometimes it will be quite obvious that a device originally developed for adults is not, in that form, suitable for some children, for example, when a particular type of implanted device is clearly too large for infants and toddlers. Other times problems with pediatric use of a device—such as more rapid or intense inflammatory reactions to implant materials than seen with adults—will not be evident during initial research and early clinical use.

It is important to recognize that while children may experience the benefits of a successful medical treatment for longer periods than older adults, they likewise may suffer the negative consequences of treatments or adverse events for many more years. As a case in point, disturbances in cardiorespiratory function at young ages may have lifelong neurological consequences, which is an argument for early intervention as well as for long-term monitoring of the consequences of device use and other interventions that may create such disturbances. Furthermore, if medical treatments interfere with growth and development, affected children may never completely "catch up." For example, some devices for treatment of scoliosis are used in conjunction with a spinal fusion process that limits further growth of the spine and surrounding structures, including the rib cage. In young children, such a limitation in thoracic growth can even prove fatal if the lungs are unable to grow and develop sufficiently.

Although medical devices and associated surgical and medical procedures can often correct medical problems and allow children to live normal and active lives, not all problems can be fully corrected, and some children saved in infancy are still expected to die in adolescence or early adulthood.

Moreover, for many children with severe medical conditions, decisions about treatment are not limited to a one-time surgery or other episode of treatment. Rather, the balancing of potential benefits and harms is ongoing as new options for treatment are proposed or the shortcomings of past interventions are revealed.

Beyond treatment decisions, parents weigh risks in structuring their child's daily life and determining the degree to which a tightly controlled, medically monitored environment should be moderated to allow a more normal childhood experience. For example, parents weigh the risk of damage to an implant against the opportunity for a child to play sports with his or her peers.

Often parents and clinicians must make decisions in the absence of good evidence about the relative safety and effectiveness of medical devices and procedures. Many complex medical devices used with children have not been systematically evaluated in pediatric populations. Even for adults, who are the typical subjects of clinical trials involving devices, uncommon problems may not be evident in clinical trials used to support applications for marketing approval. The clinical studies undertaken in support of a product's approval for marketing are usually conducted for relatively short periods in carefully controlled populations that do not fully represent the population of expected users (e.g., patients with multiple health conditions). For that reason, once medical products enter the market, government health agencies, clinicians, manufacturers, and others sometimes continue to study them for longer periods and with broader populations. In certain circumstances, the U.S. Food and Drug Administration (FDA) can require such studies. Policymakers have also created requirements for manufacturers, health care facilities, and others to report problems—adverse events—that are caused by or associated with legally marketed drugs, devices, and other medical products.

Until 1976, federal officials had limited authority to regulate the safety or effectiveness of medical devices. In that year, Congress added the Medical Device Amendments (P.L. 94–295) to the Federal Food, Drug, and Cosmetic Act (P.L. 75–717). By this step, Congress acknowledged the increasing sophistication and importance of medical device technology while also recognizing that both the benefits and the risks of this advanced technology warranted more systematic attention by FDA, manufacturers, and others.

In the past decade, with enactment of the FDA Modernization Act of 1997 (P.L. 105–115) and the Medical Device User Fee and Modernization Act of 2002 (P.L. 107–250), Congress streamlined certain regulatory procedures for medical devices. The 2002 legislation also included several provisions related to pediatric uses of devices, one of which called for this

report on postmarket surveillance of medical devices used with pediatric populations.

Postmarket surveillance of medical devices used with children is a little-investigated topic. Again, this is partly because the market for most medical products is concentrated among adults, especially older adults, so attention tends to follow clinical and market realities. Moreover, assessments and discussions of medical product regulation and patient safety tend to focus more on pharmaceuticals than on medical devices. Thus, pharmacoepidemiology is a relatively well-established area of epidemiologic inquiry while medical devices epidemiology is not. In the device arena, no readily identified organizations exist in parallel to the International Society for Pharmacoepidemiology, the International Society for Pharmacovigilance, or the Academic Programs in Pharmacoepidemiology. (These organizations devote some attention to device epidemiology, but it is not a major focus.) In addition, discussions of medical product regulation—for drugs and vaccines as well as medical devices—have tended to concentrate on the regulatory requirements and processes related to the approval or clearance of products for marketing rather than on the subsequent evaluation or surveillance of their performance.

It is appropriate to put a high priority on keeping unsafe and ineffective medical devices and other products from entering the market in the first place. It is also reasonable to ask whether the system of postmarket surveillance established under the Federal Food, Drug, and Cosmetic Act provides adequate safeguards for the use of medical devices once the devices have been approved for marketing. This report considers that question as it relates to children specifically.

As the committee that developed this report reviewed the literature, consulted knowledgeable individuals, and considered the questions before it, several themes emerged. They are:

1. *Children and their families benefit from safe, effective medical devices.* Timely access to such devices prevents premature deaths and significantly improves the quality of life for children and their families.

2. *Systematic attention to children's needs and characteristics is important in medical device design, use, and evaluation because children differ from adults in important ways.* For devices developed primarily for use with adults but with expected or possible pediatric uses, such attention can encourage the early identification of potential pediatric benefits and harms and the early consideration of modifications in the design or use of a medical device that will minimize risks and safeguard child patients. In addition, long-term studies may be necessary to understand developmental effects and the long-term balance of benefits and harms of pediatric use of long-term implants and certain other devices.

3. *An effective regulatory program for evaluating and monitoring the safety of medical devices in general is a necessary foundation for efforts to safeguard children in particular.* This basic foundation of device regulation then requires the addition of pediatric expertise, guidelines, and other resources.

4. *The regulation of medical devices reasonably differs from the regulation of drugs.* Medical devices are more variable than drugs in their mode of operation, range of function, dependence on user skills, and potential for harm. Many are simple and very low risk. For some complex devices, the use of conventional randomized, controlled trials to provide evidence of safety and effectiveness may not be feasible or ethical. In addition, much device innovation and development is characterized by ongoing product modification and improvement with a relatively rapid rate of product turnover, which may complicate some aspects of long-term monitoring and evaluation of safety and effectiveness.

5. *A careful assessment of medical device regulations weighs potential positive and negative outcomes, including whether the potential negative effects of a regulation are acceptable.* Just as the balance of potential benefits and harms should be considered when medical devices are reviewed, so should policymakers weigh the potential outcomes of regulations and consider possible unintended and unwanted consequences, for example, the discouraging of beneficial innovations and refinements in medical devices.

6. *The shift of medical device use from institutions to homes, schools, and the community complicates postmarket surveillance.* The migration of care out of the hospital into patient homes has brought many benefits, but it also presents risks as families and patients have taken on many roles in the operation, maintenance, and troubleshooting of complex medical devices that were formerly performed by health care professionals. In addition, for complex devices now used in the home, the opportunity and responsibility for identifying and reporting possible device-related adverse events has shifted, in considerable measure, to patients, families, office-based physicians, home care nurses, home health agencies, and even school personnel. Of these groups, only home health agencies have legal obligations for reporting adverse events. Surveillance programs have yet to adjust to these realities.

7. *Medical device safety is a shared responsibility.* No matter how successful, government regulation of medical devices is not sufficient in itself to safeguard children or adults who use medical devices. Clinicians, health care providers, engineers, manufacturers, researchers and research funding agencies, patients and families, consumer groups, and others have central roles to play. Regulations backed by both incentives and sanctions do, however, contribute as part of a larger system of ethical, financial, professional, and other influences that support safe, effective health care.

ORIGIN OF STUDY TASKS AND OVERVIEW OF REPORT

In 2002, Congress passed the Medical Device User Fee and Modernization Act. The main focus of this legislation was the establishment of a system of user fees, similar to that already adopted for drugs, to support the more expeditious review by FDA of applications by manufacturers for approval to market devices. The legislation also included three provisions related to medical devices with possible pediatric applications. One called for pediatric expertise, when appropriate, in the review of applications for FDA approval to market a medical device (Section 210). A second provision directed the Secretary of the Department of Health and Human Services to provide guidance on the kind of information needed to assure the safety and effectiveness of medical devices intended for use with children and to protect children involved in clinical studies of such devices (Section 213).

A third section called for a study by the Institute of Medicine (IOM) to assess whether "the system under the Federal Food, Drug, and Cosmetic Act for the postmarket surveillance of medical devices provides adequate safeguards regarding the use of devices in pediatric populations" (Section 212). The study was also to examine

- the FDA's monitoring and use of adverse reaction reports, registries, clinical studies, and other postmarket surveillance activities;
- the adequacy of FDA's monitoring of commitments for further clinical studies made by manufacturers at the time of approval of specific medical devices;
- the adequacy of postmarket surveillance studies to evaluate how children's active lifestyles may affect failure rates and longevity for implanted devices; and
- the length of postmarket surveillance studies of implanted devices, including whether studies continue long enough to evaluate the impact of children's growth and development given the expected length of time that a child will have an implant.

Together, these legislative provisions constituted the statement of task and charge to the IOM, which is the health policy arm of the National Academy of Sciences. The IOM appointed a 13-member committee of experts to prepare this report.

Given its origins, one audience for this report is legislative and administrative policymakers and those who advise them. The report does not, however, assume technical knowledge of medical device regulation. It likewise does not assume expertise in pediatric medicine or medical device design or use. It is meant to be credible to technical experts but understandable to a broader audience, including consumer and patient advocacy groups. Parents and the general public are not primary audiences, although

the committee has sought examples that would be meaningful and understandable to general readers.

This report often focuses on complex devices that are implanted in the body for extended periods (e.g., pacemakers) or that can be expected to have serious health consequences if they fail (e.g., mechanical ventilators). Even relatively simple devices can, however, cause injury and even death due either to errors in their use or to shortcomings in their design, manufacture, distribution, maintenance, or instructions for use. For example, in 2002, FDA announced the Class I (high priority) recall of a bassinet with a drop-leaf work surface that could and had collapsed when used for the unintended purpose of holding an infant (FDA, 2002j). That same year, FDA reported the Class I recall of a foam-tipped oral swab following a report that the tip had dislodged and blocked a patient's airway (FDA, 2002g). Regulatory and other strategies to protect children must also include means to detect and prevent harm from less complex and less intrinsically risky medical devices.

The remainder of this chapter defines a number of the concepts and terms included in the legislative charge for this IOM study. It also provides a brief overview of the history of medical device regulation and its context. Chapter 2 examines the rationale for particular attention to the special characteristics of children when medical devices are designed, evaluated, regulated, and used. The regulatory framework for postmarket surveillance is reviewed in Chapter 3.

Chapter 4 examines the nature, reporting, and analysis of adverse device events, including advantages and limitations of adverse event reporting as a surveillance tool. It includes a number of illustrative vignettes that depict the diversity of adverse device events involving children. Chapter 5 reviews FDA's monitoring and reporting of manufacturers' fulfillment of commitments for postmarket studies required by FDA, and Chapter 6 considers the adequacy of postmarket surveillance studies to assess the effects of children's activity levels and growth and development on device performance. Beyond the recommendations presented in the preceding three chapters, Chapter 7 offers a more comprehensive view of FDA postmarket surveillance and its place in a broader system of shared responsibilities for improving the quality of health care and protecting adult and child patients from harm.

This report also includes several appendixes. Appendix A describes the committee's information collection strategies. Appendix B provides an illustrative list of medical devices used exclusively or frequently with children. Appendix C reviews the nature of medical device innovation. Appendix D focuses on methodological issues for postmarket surveillance. Appendixes E and F present case studies of surveillance issues related to two complex devices—cerebrospinal fluid shunts and cochlear implants. The final appendixes provide a glossary and committee biographies.

SELECTED CONCEPTS AND DEFINITIONS

Discussions of medical device regulation are replete with legal and technical terminology that is unfamiliar to most audiences but reflects the complexity of medical products and their regulation. This section defines a number of terms found in the study's statement of task as well as some related terms. Later chapters include more definitions. Chapter 2, for example, discusses the concepts of children's active lifestyles and growth and development as they relate to certain device therapies, especially those involving implanted devices.

Pediatric Population, Children

Pediatrics refers to the health care of children. As part of guidance on premarket assessment of pediatric medical devices, FDA's Center for Devices and Radiological Health (CDRH) stated that it considered *pediatric use* "to be any use of a medical device in a pediatric population . . . in which there is a primary pediatric indication. General indications, where considerable pediatric application is anticipated, are also included in this definition" (FDA, 2004p, p. 5). This report generally refers to devices with pediatric uses rather than to pediatric devices.

The term *pediatric population* may refer to all children or to a subgroup of children who share certain characteristics (e.g., a diagnosis or the use of a medical device). In broad usage, *children* are individuals, including infants and adolescents, who are not considered to be adults. From a legal perspective, nearly all states consider individuals aged 18 or above to be adults, although states may allow younger individuals to make decisions about medical treatment and other matters as adults under certain circumstances (English and Kenney, 2003; Campbell, 2004). In recent guidance on premarket assessment of devices used with children, CDRH has expansively defined children as those under the aged of 21, arguing that this upper age limit may be useful for some devices and clinical studies (FDA, 2004p). In a narrower usage, a child is an individual who is between the periods of infancy and adolescence. As discussed further in Chapter 2, definitions of these periods vary, even within FDA (see Chapter 2).

Medical Device, Implanted Device, Combination Product

Definitions

The key statutory distinction between a drug and a device is that a device does not work primarily through chemical means and does not

depend on metabolic action. As defined in the U.S. Code (21 USC 321(h)), a medical device is:

> an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including any component, part, or accessory which is:
>
> • recognized in the official National Formulary, or the United States Pharmacopeia, or any supplement to them;
> • intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals; or
> • intended to affect the structure or any function of the body of man or other animals, and which does not achieve its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of its primary intended purposes.

Consistent with scientific and technological developments, a more recent definition adopted by the European Union (EU) explicitly excludes products that work by immunological mechanisms. The EU definition also includes software necessary for a device to operate properly.[1] The EU definition goes beyond diseases to recognize explicitly that devices are used in connection with injuries and disabilities as well as for contraception. In addition, the definition acknowledges the importance of products such as implants and prostheses that replace or modify the anatomy.

FDA regulations use two slightly different definitions of *implants* or *implanted devices*. The regulations related to investigational devices (see Chapter 3) define an implant as "a device that is placed into a surgically or naturally formed cavity of the human body if it is intended to remain there for a period of 30 days or more" (21 CFR 812.3(d)). The regulations on medical device tracking (see Chapter 3) refer to implanted devices as those "intended to be placed into a surgically or naturally formed cavity of the human body for more than 1 year to continuously assist, restore, or replace

[1]Specifically, the EU defines a device as "any instrument, apparatus, appliance, material or other article, whether used alone or in combination, including the software necessary for its proper application intended by the manufacturer to be used for human beings for the purpose of: (a) diagnosis, prevention, monitoring, treatment or alleviation of disease; (b) diagnosis, monitoring, treatment, alleviation of or compensation for an injury or handicap; (c) investigation, replacement or modification of the anatomy or of a physiological process; (d) control of conception; and which does not achieve its principal intended action in or on the human body by pharmacological, immunological or metabolic means, but which may be assisted in its function by such means" (EU, 2003, p. 5; see also FDA, 2004o).

the function of an organ system or structure of the human body throughout the useful life of the device" (21 CFR 821.3(f)).[2]

An increasing number of medical products combine elements such as a drug and device or a biological product and device.[3] Examples of such products include insulin pumps (computer-controlled, wearable devices that deliver periodic doses of insulin as programmed by the patient) and drug-eluting stents (devices that hold open blood vessels and are coated with slow-release drugs to reduce new blockage of the vessels). As defined by FDA, a c*ombination product* consists of two or more regulated components that are physically combined or linked, packaged together as a single unit, or packaged separately but required to be used together (21 CFR 3.2(e)). The product's primary mode of action determines which unit of FDA has primary jurisdiction over the product (21 CFR 3.4; FDA, 2004e). Thus, because the primary action of the drug-eluting stent is to open the blood vessel, it is primarily regulated by CDRH. In contrast, a drug-eluting disk that delivers chemotherapy agents for brain tumors is primarily regulated by the Center for Drug Evaluation and Research.

Although this report often will refer to a medical device, "a" medical device may actually be composed of several device subsystems or individual devices that work together as a system to achieve the desired effect. For example, a left ventricular assist device that helps the heart beat recently received special FDA approval (a humanitarian device exemption or HDE as described in Chapter 3) for use with children. The device is described as consisting of four major subsystems—a pump, an external controller, a clinical data acquisition system, and a patient home support system—as well as assorted accessories, including batteries, a battery charger, and a shower kit to protect the device during showering (H030003, FDA, 2004b). The pump subsystem itself consists of the pump housing within which three components move blood through the pump, a titanium inlet/inflow cannula

[2]An EU directive defines an implantable device as a type of invasive device "which is intended: to be totally introduced into the human body, or to replace an epithelial surface or the surface of the eye, by surgical intervention which is intended to remain in place after the procedure. Any device intended to be partially introduced into the human body through surgical intervention and intended to remain in place after the procedure for at least 30 days is also considered an implantable device" (EU, 2003, p. 45). In an earlier directive, an "active implantable medical device" ("active" meaning, essentially, that the device depends on electrical energy) is defined as a device "intended to be totally or partially introduced, surgically or medically, into the human body or by medical intervention into a natural orifice, and which is intended to remain after the procedure" (EU, 1990, p. 17).

[3]Biologics include an array of products such as vaccines, blood and blood products, human tissues and cellular products (such as stem cells), and gene therapy products. The Center for Biologics Evaluation and Research at the FDA regulates biologics and certain closely related drugs (e.g., anticoagulants packaged in plastic containers for collecting blood) and devices (e.g., those used in collecting and safeguarding blood) (FDA, 2004m).

(tube), a Dacron outflow graft, an implanted probe to measure blood flow, and a cable to connect the implanted pump to the external battery pack and controls. Each component must function safely and effectively in concert with the other components.

Device Classes, Approval, Clearance

Since 1976, the legal classification of medical devices has provided for three classes of devices based in large measure on the risk they pose. Class I devices, which include such mundane items as tongue depressors, lice combs, toothbrushes, and bedpans, are the least regulated. They do not require review by FDA before they can be legally marketed. Class III devices, which include implants and other high-risk devices, are the most regulated. For these devices, manufacturers must submit clinical evidence of safety and effectiveness and secure *approval* by FDA prior to marketing. Manufacturers of Class II devices face an intermediate level of regulation, including a *clearance* process that usually does not require the submission of clinical data. These three classes of devices and their regulation are discussed further in Chapter 3.

In addition to these three broad classes, FDA uses a more detailed nomenclature system—involving some 1,700 categories of medical devices—to support its regulatory activities. FDA is participating in efforts to "harmonize" device nomenclature internationally. Much of that work now focuses on the possible merger of two systems, the Universal Medical Device Nomenclature System (UMDNS) developed by ECRI (formerly the Emergency Care Research Institute) in the United States and the Global Medical Device Nomenclature (GMDN), which is owned by the European Standards Organization (Lumpkin, 2004). To illustrate this kind of detailed device classification scheme, Appendix B lists a subset of terms from the UMDNS for devices that have uses with children. As discussed in Chapters 4 and 6, this level of detail, while useful for some purposes, does not reach the level of detail about a specific device (e.g., lot number, model, brand) necessary for some safety and surveillance purposes.

Between the detail of the UMDNS and GMDN and the generality of the three broad FDA risk-related device classifications are other ways of categorizing devices that are useful for certain objectives.[4] For example, for purposes of establishing scientific panels to review devices, FDA regulations

[4]In addition to FDA classifications of devices, the U.S. Department of Commerce classifies medical devices into five categories. These categories, which are part of the North American Industrial Classification system, are surgical and medical instruments; surgical appliances and supplies; dental equipment and supplies; irradiation apparatuses; and navigational, measuring, electromedical, and control instruments.

group devices into 16 categories based mostly on medical specialty (Box 1.2) (21 CFR 862–892).

Safeguard, Safety, Risk, Harm, Hazard, Benefit, Effectiveness, Efficacy

A *safeguard* protects someone or something from harm. FDA's statute and regulations do not define *safe* or *safety* as such but do describe criteria for determining that a medical product is safe. Specifically, "there is reasonable assurance that a device is safe when it can be determined, based upon valid scientific evidence, that the probable benefits to health from use of the device for its intended uses and conditions of use, when accompanied by adequate directions and warnings against unsafe use, outweigh any probable risks" (21 CFR 860.7(d)(1)). There should also be adequate demonstration "of the absence of unreasonable risk of illness or injury associated with the use of the device for its intended uses and conditions" (21 CFR 860.7(d)(1)).

Thus, from a device regulation perspective, *safety* is relative. A product with great expected benefits and significant (but not unreasonably high) risks may be judged to be safe, while a product with lesser expected benefits and the same level of risk may be judged unsafe.

Safety is also relative in other respects. What is safe for an adult may not be safe for a child. What is safe for an adolescent may not be safe for an infant.

Few if any medical products are completely free from risk. *Risk* refers to a potential harm or the potential of an action or event to cause harm. Specific risks can be characterized along several dimensions, including the probability of a given harm as well as its likely severity and duration. A *harm* is a hurtful outcome of an event or action. A *hazard* is a potential

BOX 1.2
Categories of Medical Devices for Purposes of FDA Scientific Review

Anesthesiology
Cardiovascular
Clinical Chemistry and Clinical Toxicology
Dental
Ear, Nose, and Throat
Gastroenterology and Urology
General and Plastic Surgery
General Hospital and Personal Use
Hematology and Pathology
Immunology and Microbiology
Neurological
Obstetrical and Gynecological
Ophthalmic
Orthopedic
Physical Medicine
Radiology

SOURCE: 21 CFR 862–892.

source of harm. Harms may be immediate or long term and may be common and anticipated or rare and unexpected.

A *benefit* is a positive or valued outcome of an action or event. A *potential benefit* is a positive but uncertain outcome, for example, the desired result of an experimental intervention.

Just as safety is not explicitly defined, FDA's statute and regulations do not define *effectiveness* explicitly but instead set forth criteria for determining effectiveness. Specifically, "[t]here is reasonable assurance that a device is effective when it can be determined, based upon valid scientific evidence, that in a significant portion of the target population, the use of the device for its intended uses and conditions of use, when accompanied by adequate directions for use and warnings against unsafe use, will provide clinically significant results" (21 CFR 860.7(e)(1)). As is true for safety, a device that is effective for an adult may not be effective for a child.

Effectiveness is sometimes differentiated from *efficacy*, with the former term used to describe the achievement of desired results in actual practice and the latter to the achievement of such results in controlled studies. In 1998 guidance on clinical evidence of effectiveness for drugs and biological products, FDA states that as used in that document, "the term efficacy refers to the findings in an adequate and well-controlled clinical trial or the intent of conducting such a trial and the term effectiveness refers to the regulatory determination that is made on the basis of the clinical efficacy and other data" (FDA, 1998f, p. 1).

Adverse Event, Close Call or Near Miss, Device Failure or Malfunction, Error

An *adverse event* is an instance of harm during patient care or research that is not the result of the individual's disease or medical condition. Thus, a death due to cancer while a patient is receiving chemotherapy through an infusion pump is an adverse outcome but *not* an adverse event. A death due to the incorrect setting of an infusion pump for chemotherapy is both an adverse outcome and an adverse event. The charge to the committee refers to adverse reactions, but FDA refers to adverse events. This report follows FDA usage.[5]

Adverse events are sometimes defined to include events that have the potential to cause harm, such as *close calls* or *near misses* that could have resulted in harm but did not. To cite an example, when a device malfunc-

[5]The Joint Commission on the Accreditation of Healthcare Organizations uses another term, "sentinel event," by which it means "an unexpected occurrence involving death or serious physical or psychological injury, or the risk thereof" *and* requiring prompt investigation (JCAHO, 2005a, unpaged).

tions but a caregiver notices it and responds quickly enough to avert injury, that event is a close call or near miss.

Adverse events and close calls may result from a device failure or malfunction. As defined in federal regulations, a *device failure* "means a device does not perform or function as intended, and includes any deviation from the device's performance specifications or intended use" (21 CFR 822.3(c)). Elsewhere, the regulations define *device malfunction* in similar terms as "the failure of a device to meet its performance specifications or otherwise perform as intended" (21 CFR 803.3(n)). Devices may fail or malfunction in myriad ways—breaking outright, leaking, catching fire, clogging, crimping, warping, experiencing software "bugs," and otherwise deviating from intended performance.

Adverse events may also occur when devices are improperly used, operated, assembled, monitored, stored, maintained, or selected by health care workers, families, or patients. These events are kinds of health care *errors*, which another IOM report has defined as "the failure of a planned action to be completed as intended (i.e., error of execution) or the use of a wrong plan to achieve an aim (i.e., error of planning)" (IOM, 2000c, p. 28). Because errors in the use of medical devices may reflect flaws in the design of the devices and because reference to user errors may contribute to a counterproductive culture of blame within health care organizations, FDA tends now to refer to *use error* rather than user error.

The reporting of adverse events and device malfunctions is discussed further in Chapters 3 and 4. The focus of these discussions is on adverse events detected in normal patient care rather than in research. The reporting of adverse events in research is governed by separate policies.

Premarket and Postmarket

As with many government regulatory agencies, FDA has developed a specialized vocabulary to describe its responsibilities, activities, organizational units, and regulated entities. Much of this terminology has its basis in statutory language and distinctions. In referring to *premarket* and *postmarket* rather than *premarketing* and *postmarketing* activities, this report follows the statutory language that provided for this study and the usual (but not invariable) practice of FDA in describing activities that occur either prior to or following the entry of a medical product into the market.

Premarket regulatory processes include evaluations, decisions, and other activities that occur before the marketing of a medical product consistent with legal requirements (see Chapter 3). Thus, the development and evaluation of information about a device's safety and effectiveness and the approval or clearance of a product for marketing are premarket activities.

Likewise, the authorization to test an unapproved device with humans is a premarket activity.

Postmarket evaluations, activities, and decisions occur after regulatory approval, clearance, or registration of a medical product for marketing. As discussed further in Chapter 3, the major device-related postmarket responsibilities of FDA involve its programs for adverse event reporting and focused surveillance or follow up of selected products, sometimes including required clinical studies.

Surveillance and Surveillance Tools

From a broad public health perspective, *surveillance* may be defined as the "ongoing, systematic collection, analysis, interpretation, and dissemination of data regarding a health-related event for use in public health action to reduce morbidity and mortality and to improve health" (CDC, 2001, p. 2). Most but not all surveillance involves unwanted events such as deaths and injuries or hazardous or potentially hazardous situations such as exposure to unsafe medical products, communicable diseases, toxic substances, or unsafe workplaces (see, e.g., Halperin et al., 1992; Tilson, 1992; Friis and Sellers, 2004).

Broadly, then, *postmarket surveillance of medical devices* refers to programs that seek to protect public health by systematically collecting, analyzing, and communicating information about events involving or potentially involving legally marketed medical devices. More narrowly, Section 522 of the Federal Food, Drug, and Cosmetic Act uses the term *Postmarket Surveillance* to describe one type of surveillance, specifically, activities that FDA may—after a device is approved or cleared for marketing—require manufacturers to undertake to gather safety and, sometimes, effectiveness information for a small group of Class II and Class III devices (21 USC 360(l)). As described by FDA and discussed further in Chapter 3, the primary objective of Section 522 Postmarket Surveillance "is to study the performance of the device after marketing as it is to be used in the general population for which it is intended . . . [with a focus on] morbidity or mortality . . . [and on] device failure and its attendant impact on the patient" (FDA, 1998b, unpaged). *Unless otherwise noted, this report uses the term postmarket surveillance in its broad sense* (and indicates the narrower usage by referring to *Section 522 Postmarket Surveillance*).

In addition to studies ordered after a device has been approved or cleared for marketing, surveillance studies may be undertaken to investigate important unanswered questions that exist at the time a device is considered for approval. As a condition of approving a device, FDA can require that manufacturers collect more information about the safety or effective-

ness of a device. This report uses the term *postmarket studies* or *postmarket study commitments* to refer collectively to condition-of-approval studies and Section 522 studies that are ordered after a device enters the market.

Some postmarket studies continue to follow individuals who participated in the clinical trials or other studies that were used to support an application for FDA approval or clearance of a medical device.[6] Other postmarket studies involve registries of new patients. A *registry* is a system for collecting information about a class of individuals or patients who have in common a disease, injury, condition, medical procedure or product, or similar characteristic. The term registry is sometimes used narrowly to refer to the database itself and sometimes more broadly to refer to analyses and studies based on registry information. For the latter, this report generally refers to *registry studies* or *registry-based studies*.

A major tool of FDA postmarket surveillance is an *adverse event reporting system* for collecting and analyzing information about product failures or harms related to or potentially related to medical products. For medical devices, the emphasis is on the reporting of device failures and malfunctions and device-related deaths or serious injuries. As discussed in Chapters 3 and 4, the primary FDA program of adverse event reporting for medical products, MedWatch, relies on *passive* surveillance; that is, it awaits reports that manufacturers, health care facilities, health care professionals, and others decide to submit. In addition, FDA has created the Medical Device Safety Network (MedSun, formerly known as the Medical Product Surveillance Network), a pilot program that involves selected hospitals and nursing homes). This program includes some elements of *active* surveillance, for example, a request that all or some participating institutions collect information on a specific problem or event.

In addition to surveillance undertaken or directed by FDA, manufacturers for implanted devices such as pacemakers and defibrillators conduct active surveillance of these products. Health care providers, some state governments, accrediting groups, and various other private organizations also have surveillance programs for identifying patient safety problems, although medical devices usually do not figure prominently in these programs.

Certain activities to build additional knowledge about the safety or effectiveness of a marketed medical device—for example, some clinical tri-

[6]A guidance document on clinical trials involving medical devices cites this definition of clinical trial: "a prospective study comparing the effect and value of intervention(s) against a control in human subjects" (Friedman et al., 1985; cited in FDA, 1996c). Many clinical studies used to support FDA approval of medical devices do not have prospective control groups. Chapter 6 and Appendix D discuss research strategies and issues.

als sponsored by the National Institutes of Health (NIH)—are not normally described as surveillance. Similarly, manufacturer studies to support the approval of *new* indications for the use of a device (e.g., use for a different medical condition) are not usually viewed as surveillance, although they may generate important information about device safety or effectiveness that is relevant to previously approved indications.

If postmarket surveillance identifies safety problems involving a device or its use, manufacturers may recall the product, modify its design or manufacturing process, or change information about how or for whom it should be used. Manufacturers and regulators may advise clinicians, health care organizations, and sometimes patients or consumers to cease using the product, limit its use to certain patient groups or clinical purposes, or change processes for using the product (e.g., by adjusting equipment settings in different ways).

EVOLUTION OF MEDICAL DEVICE REGULATION

Regulation of medical devices has tended to lag behind regulation of pharmaceuticals.[7] When Congress passed the original Pure Food and Drugs Act (P.L. 59–384) in 1906, it banned interstate and foreign commerce in misbranded and adulterated drugs, food, and drinks—but not medical devices. The legislation provided for the seizure of prohibited products and for fines and imprisonment for those engaging in prohibited commerce. The legislation was the culmination of years of advocacy and agitation for federal action to protect consumers from impure, unsafe, and mislabeled foods and medicines. (Table 1.1 provides a time line of significant events in the evolution of medical product regulation in the United States.)

Although the 1906 Act did not cover devices, the U.S. Postal Service (under its general authority to act against mail fraud) could pursue cases of mail order fraud involving devices. For example, a 1929 FDA report mentioned cooperation with the Postal Service in cases involving "a cap device alleged to grow hair, and a supposedly electronic belt and insoles for the treatment of rheumatism and kidney ailments" (as quoted by Hutt, 1989, p. 101).

FDA first received authority to regulate medical devices in the 1938 Federal Food, Drug, and Cosmetic Act. Among many other important provisions, that legislation authorized factory inspections, directed that drug and device labels provide adequate directions for safe use, extended controls to cosmetics, and eliminated the requirement that fraud be proved in

[7]This discussion draws on several sources: Janssen, 1981a,b,c; GAO, 1989, 1997; Hutt, 1989; Hutt and Merrill, 1991; Merrill, 1994; Munsey, 1995; Karuga, 2003; and AdvaMed, 2004.

TABLE 1.1 Selective Time Line of Key Dates in Development of the Food and Drug Administration's Regulatory Authority over Medical Products, Especially Devices

1848	Drug Importation Act. Intended to stop the import of adulterated drugs.
1902	Biologics Control Act. Intended to protect the purity and safety of serums, vaccines, and similar products used to prevent or treat diseases in humans.
1906	Pure Food and Drugs Act. Provided first major federal regulation of drugs. Did not apply to medical devices. (Fraudulent medical devices covered under postal fraud regulations.)
1938	Federal Food, Drug, and Cosmetic Act. Required premarket review of new drugs for safety. Gave FDA authority over adulterated or misbranded therapeutic devices.
1940	Food and Drug Administration moved from the Department of Agriculture to predecessor of the Department of Health and Human Services.
1941	Insulin Amendment. Required FDA to test and certify purity and potency of insulin.
1944	Public Health Service Act. Covered a broad spectrum of health concerns, including regulation of biologics.
1954	Voluntary program of drug reaction reporting. Created through collaboration of FDA with American Society of Hospital Pharmacists, the American Association of Medical Record Librarians, and (later) American Medical Association.
1962	Drug Amendments (Kefauver-Harris). Expanded FDA responsibilities to ensure drug safety and effectiveness. Effectiveness must be proved by "substantial evidence."
1966	Fair Packaging and Labeling Act. Required all products in interstate commerce to be honestly and informatively labeled, including medical devices.
1973	FDA guidelines for voluntary reporting of adverse events.
1976	Medical Device Amendments. Redefined "device." Required manufacturers to give FDA notification of new devices introduced to market. Gave FDA authority to describe good manufacturing practices, to approve and ban certain devices before marketing, and to require notification, replacement, or refund by makers of defective products.
1984	Medical Device Reporting (MDR) regulations. Required device manufacturers and importers to report device-related deaths, serious injuries, and malfunctions to FDA.
1990	Safe Medical Devices Act. Required facilities using medical devices to report incidents related to a death, serious illness, or serious injury to FDA or manufacturers. Provided for mandatory Postmarket Surveillance by manufacturers for implanted or life-supporting devices that might cause death or serious harm. Gave FDA authority to impose civil penalties and, under certain circumstances, recall devices.
1992	Global Harmonization Task Force established to promote international harmonization in regulation of medical devices.
1992	Medical Device Amendments. Required semi-annual reports from user facilities. Expanded requirements for registration, certification, documentation, reporting, and surveillance of medical devices.
1993	MedWatch created. Allowed consumers and health care professionals to report adverse events.

(continues on next page)

TABLE 1.1 continued

1997	Food and Drug Administration Modernization Act. Accelerated FDA review of devices, regulated advertising of devices for unapproved uses.
2002	Medical Device User Fee and Modernization Act. Provided for user fees for premarket reviews of medical devices. Included provisions for this and other pediatric studies or analyses.
2004	Medical Devices Technical Corrections Act. Required a report on barriers to the availability of devices intended for children and expanded provision for electronic labeling.

SOURCES: Hutt, 1989; Merrill, 1994; Higgs, 1995; FDA, 1999d, no date; Flannery, 2002; Whitmore, 2004.

cases of false product claims. It also required that new drugs—but not new devices—be shown to be safe before they were marketed.

As described in one review of the history of device regulation, "[p]aradoxically, just after the FDA was given adequate statutory authority to police the safety and labeling of devices, a flood of fraudulent devices began to appear on the market" (Hutt, 1989, p. 105). The agency devoted considerable resources to such devices in the 1940s and 1950s.

Congress passed another broad piece of major legislation with the Drug Amendments of 1962 (P.L. 87–78, sometimes called the Kefauver-Harris Amendments for its sponsors). The legislation significantly expanded regulatory requirements for drugs but not devices. Notably, it required manufacturers to show evidence of effectiveness as well as safety before marketing, to report adverse events for marketed drugs, and to include information about risks as well as benefits in medical advertisements. Before becoming involved in clinical studies of investigational drugs, research subjects had to give their informed consent.

Proposals for the regulatory reforms of the early 1960s had originally covered medical devices, but those provisions were set aside in favor of a focus on drugs. At the time it was understood that "Congress would return to the matter of device legislation within a matter of months," but despite many calls for action, Congress waited to do so until 1976 (Hutt, 1989, p. 106). In the interim, FDA capitalized on similar statutory definitions for drugs and devices to classify certain innovative products as drugs rather than devices, and the courts acquiesced to this interpretation of the 1938 legislation. For example, the Supreme Court sustained FDA's categorization of a laboratory screening device (an antibiotic sensitivity disk) as a "drug," which made it subject to premarket regulations. The Court reasoned that "the word 'drug' is a term of art for the purposes of the Act, encompassing far more than the strict medical definition of that word. If Congress had intended to limit the statutory definition to the medical one, it could have so stated explicitly" (United States v. Bacto-Unidisk, 1969, unpaged).

Acknowledging concerns about the safety of increasingly sophisticated and complex medical devices, the Secretary of the Department of Health, Education and Welfare (now the Department of Health and Human Services) established a committee to consider the regulation of medical devices. In 1970, the committee, which was chaired by Dr. Theodore Cooper (director of what was then the National Heart and Lung Institute), recommended that regulation of devices be tailored to characteristics of devices rather than essentially copying provisions established for drugs. For example, the committee recommended that device regulation be keyed to the variability in the risks presented by different kinds of devices (Study Group on Medical Devices [Cooper Committee], 1970). The committee also undertook a literature review that identified (as reported to a congressional committee) more than 700 deaths and 10,000 injuries linked to medical devices, including 512 deaths or injuries attributed to heart valves, 89 deaths and 186 injuries linked to heart pacemakers, and 10 deaths and 8,000 injuries attributed to intrauterine devices (U.S. Congress, 1973, as cited in OTA, 1984 and Hutt, 1989).

Responding to the recommendations of the Cooper Committee, FDA conducted an inventory of medical devices then on the market. It also began work to classify medical devices based on the level of risk and appropriate regulation. The organizational unit responsible for devices became the Bureau of Medical Devices and Diagnostic Products, matching the Bureau of Drugs in organizational standing. That unit, which was merged with a unit responsible for radiological health in 1982, was renamed the Center for Devices and Radiological Health in 1984, the name that remains today.

The Medical Device Amendments of 1976 (P.L. 94–295) extended FDA authority to regulate devices. As recommended by the Cooper Committee, the legislation distinguished the specifics of device regulation from those of drug regulation in several respects, for example, creating the three-tier classification described earlier, which links regulatory requirements to risk. The 1976 legislation also gave FDA authority to create a system for reporting adverse events associated with devices. Going beyond the earlier voluntary program for reporting adverse device-related events, FDA issued regulations in 1984 that required manufacturers and importers of devices to report information indicating that a device might have caused or contributed to a death or serious injury. They were also to report malfunctions with the potential to cause death or serious injury.

The Safe Medical Devices Act of 1990 added requirements that hospitals and other "user" facilities report to FDA and manufacturers any events indicating that a device had caused or contributed to a death. It also required user facilities to report to manufacturers events suggesting that a device had caused or contributed to serious patient harm. The legislation established new requirements that manufacturers track certain kinds of

high-risk medical devices, and it gave FDA the authority to order recalls of devices under certain circumstances. It further provided that FDA direct manufacturers to conduct additional information collection activities for certain implants and other devices with the potential to cause serious harm. Although the Safe Medical Devices Act increased the scope of device regulation, it also gave FDA the authority to approve—through a Humanitarian Device Exemption (HDE)—certain medical devices for small user populations without requiring substantial clinical evidence of effectiveness. Since HDE regulations went into effect at the end of 1996, 30 HDEs have been approved, several of which provide for pediatric use.

Reflecting a growing sentiment that regulations—or the way they were administered by FDA—were interfering with the timely introduction of important new medical products, the 1997 FDA Modernization Act reversed some provisions of the 1990 legislation. It eliminated certain requirements for adverse event reporting and ended provisions for mandatory postmarket surveillance studies in favor of FDA discretion to order studies or information collection for certain kinds of devices. The legislation further focused FDA resources on higher risk devices and authorized the creation of a new adverse event reporting system based on a sample of hospitals and other user facilities.

The Medical Device User Fee and Modernization Act of 2002, which called for this IOM study, provided for a system of user fees for FDA premarket reviews. Among other provisions, the legislation directed FDA to prepare a report on the effects of and compliance with surveillance requirements. The legislation also authorized additional appropriations for postmarket surveillance activities, but Congress did not appropriate these funds.

Other FDA regulations set forth requirements for the protection of human participants involved in research on medical devices and other medical products. As briefly described in Chapter 6, these human research protection regulations include special protections for children (IOM, 2004a).

In addition to special provisions related to research involving children, Congress and FDA have directed attention to children in some other areas, mostly to expand the availability and testing of pharmaceuticals for pediatric use. Some provisions have, however, dealt either with medical devices specifically or with all products regulated by FDA. For example, the Best Pharmaceuticals for Children Act of 2002 directed FDA to create an Office of Pediatric Therapeutics to be responsible for coordinating and facilitating FDA activities that affect children and the practice of pediatrics. As discussed further in Chapter 2, the Medical Device User Fee Amendments of 2002 directed the agency to develop guidance on the assessment of medical devices used with children and to make pediatric expertise available when issues involving children arise or may arise, for example, in the review of

medical device applications or studies of medical devices. In the Medical Devices Technical Corrections Act of 2004, legislators directed FDA to report on "barriers to the availability of devices intended for the treatment or diagnosis of diseases and conditions that affect children" (P.L. 108–214, Section 3). That report was issued by FDA in fall 2004 (see Chapter 7 for a summary).

MEDICAL DEVICE REGULATION IN CONTEXT

As suggested above, the extension of FDA's regulatory authority over devices was a response to the increasing complexity and sophistication of medical devices. This increase has many causes, including the stimulus to scientific and engineering innovation provided by World War II, the post-war acceleration of public and private investments in biomedical and bioengineering research, the growth of academic medical centers, and the expansion of public and private health plans that pay for medical treatments.

Today's medical devices constitute an extremely varied category of medical products—some as simple and low risk as an infant cap, others as complex and high risk as a cardiac pacemaker. The medical device industry likewise is quite variable, as described in Appendix C. It includes small firms with a single product (or variants on a core product) and large companies with diverse product portfolios and substantial resources to devote to research and development, marketing, and government relations. Compared to the pharmaceutical industry, the device industry includes a larger proportion of small firms, and patents are less important as a source of competitive advantage. In this environment, few incentives may be present to develop, modify, and test medical devices to meet the special needs and characteristics of children, given that children constitute a relatively small market for most complex medical devices. (For further discussion, see FDA, 2004y.)

Differences between drugs and devices extend to clinical research. The classic models for medical product research were developed with drugs, not medical devices, in mind. The conventional distinctions between Phase I, II, and III clinical trials for drugs do not readily fit device trials. Instead, discussions of device trials sometimes differentiate between feasibility or pilot studies and pivotal studies.[8] As described above, clinical testing is not required for Class I and most Class II devices.

[8]In drug studies, Phase I clinical trials involve the initial test of a drug with humans—usually healthy adult volunteers—with a focus on safety of the product and its interaction with the body (e.g., whether it stimulates an immune reaction). Phase II clinical trials usually involve a larger group of participants and an assessment of efficacy as well as further evaluation of safety and adverse effects. These trials typically involve participants with a particular disease or condition. Phase III clinical trials are typically rigorous controlled clinical studies that extend efficacy and safety testing to a larger number of research participants who may be

Compared to the drug industry, the product development cycle in the device industry tends to involve a more continuous process of refinement and innovation. Instead of single molecules (and a relatively small array of formulation options such as pills or liquids), devices typically involve a number of components or features that change as a result of minor or major alterations in design, materials, manufacturing processes, or other characteristics.[9]

As illustrated in Figure 1.3, the movement from product concept to approved product typically takes many years as is also true for drugs. For both drugs and devices, the development process sometimes ends with the abandonment of a product that fails to prove itself technically, clinically, or competitively. To the extent that drugs and devices differ, the differences may warrant adaptations in regulatory and evaluation strategies. Still, the public should expect medical devices to be safe and effective and should expect FDA to fulfill its responsibilities in this regard.

In recent years, CDRH has applied a model of the medical device product cycle to guide the conceptualization and evaluation of its procedures for device evaluation and regulation (Feigal, 2002). As shown in Figure 1.4, the cycle begins with a concept followed by initial development and testing, a phase that includes consultation with FDA about the evaluative methods and information needed to support approval or clearance of the device. The cycle continues through FDA approval or clearance (if the evidence warrants) and then moves on to product marketing and commercial use. Typically, problems with a device or continued innovation and improvement lead to its eventual departure from the market, although not necessarily from clinical use or FDA surveillance. As noted above, some

randomly assigned to receive the experimental drug or a standard treatment or a placebo. (Information collection activities conducted after marketing approval are sometimes referred to as Phase IV studies or trials. Such studies are often much less rigorous and may be intended more to achieve market awareness than to build scientific knowledge.) This phase classification of clinical trials is not routinely applied to device studies. More commonly, the earliest device investigations using human subjects are termed pilot or feasibility studies, and subsequent studies are referred to as pivotal studies. Pilot or feasibility studies with a small number of human subjects provide an initial clinical assessment of device safety, an opportunity to modify the prototype device to improve performance, and, sometimes, a period of important learning about the technical process and skills required to use the device safely and effectively. Pilot studies also provide experience and information useful in designing so-called pivotal studies, which recruit larger numbers of research participants and often involve multiple study sites and centers.

[9]These changes may require FDA approval or clearance. For example, FDA recently gave supplemental approval (the 26th such approval) for the manufacturer of an electronic orthopedic device to make several changes, including switching the power source from a disposal to a rechargeable battery, changing to a backlit information display, and using a single circuit assembly board (P850007-S027, FDA, 2005).

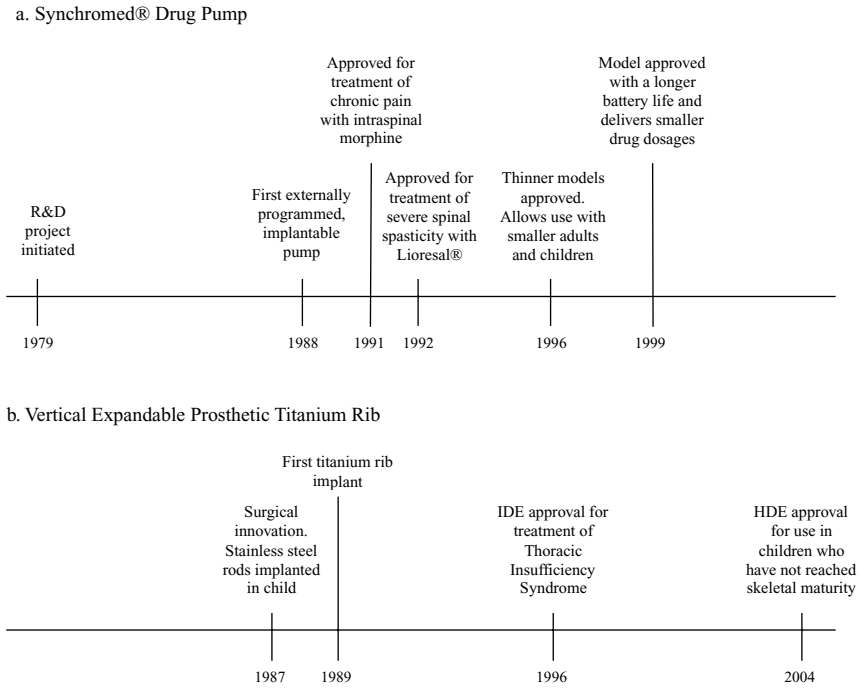


FIGURE 1.3 Time lines of key dates in development of the Synchromed® drug pump and the Vertical Expandable Prosthetic Titanium Rib (VEPTR) (Doctor's Guide, 1996; P860004-S042, FDA, 1999; H030009, FDA, 2004a; Sansom, 2004; personal communication, Paul Citron, Committee Member, November 16, 2004).

implants may remain in a patient indefinitely, and other devices may survive in hospitals, nursing homes, or home use long after better devices or other therapies have become available.

One theme of this report is that government regulation of medical devices cannot by itself safeguard children or adults who use medical devices. The availability of safe and effective medical devices and their safe and effective use depends on the knowledge, skill, creativity, and integrity of many individuals and organizations on the frontlines of clinical care and device development and production.

At the same time that attention is paid to these individuals and organizations in their own right, policymakers need to view these actors as parts of a health care system and market for medical services and products that are characterized by a strikingly complex set of structures, policies, processes, resources, ethical values, and incentives that interact in ways that are often difficult to anticipate. Thus, those creating or modifying regulatory

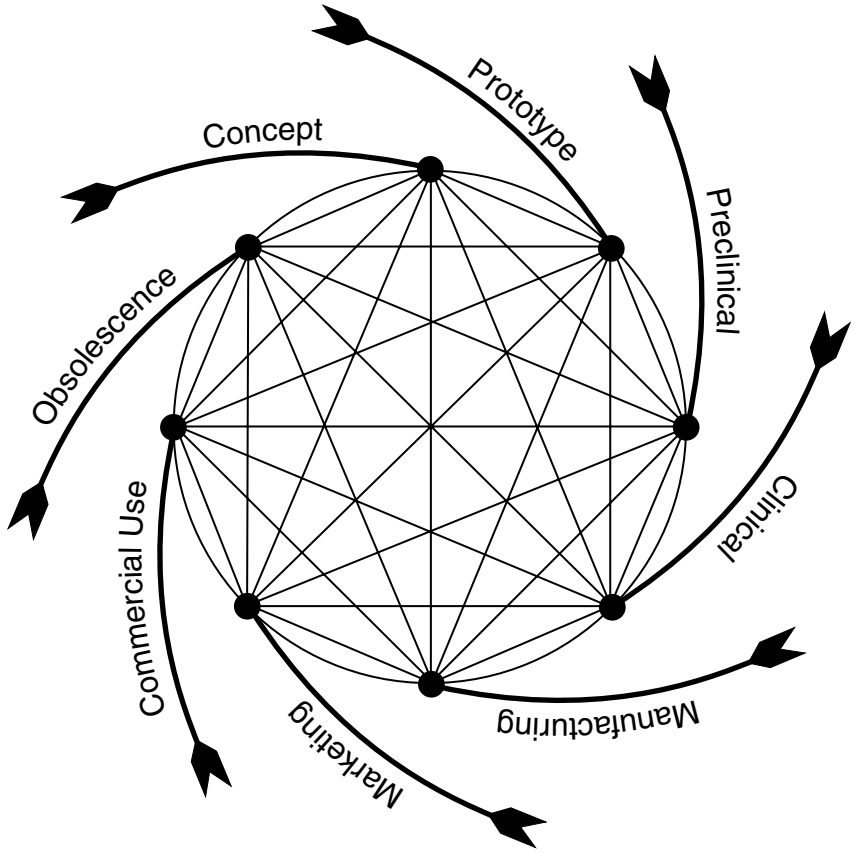


FIGURE 1.4 Total product life cycle for medical devices (Feigal, 2002).

and other public policies should consider how such interactions may support or compromise the achievement of social and policy goals. That requires looking beyond FDA policies to, for example, the research priorities of NIH, the coverage and reimbursement policies of Medicare and other health plans, and the patient safety initiatives of public agencies such as the Agency for Healthcare Research and Quality and private agencies such as the Joint Commission on the Accreditation of Healthcare Organizations. It also requires an understanding of the processes of device innovation and the characteristics of the device industry, and an appreciation of the potential for policies to have unintended and unwanted effects.

The broad goal of applying a systems perspective to health care is to improve the quality of care by understanding features of organizational and social systems that help individuals and groups perform correctly and con-

sistently to achieve desired results. In the context of medical device safety and postmarket surveillance, a systems perspective also means looking beyond individual errors with medical devices to identify the human factors and system characteristics that contribute to such errors.

Another dimension of improving the quality of care involves strengthening the evidence base for clinical practice *and* the translation of that science base into guidelines and other tools, processes, or systems that successfully influence practice. Many common medical practices—for example, a range of unlabeled uses of drugs and medical devices with children—have not been subjected to systematic clinical investigation to document their safety and effectiveness in practice.

In response to the particular shortfalls in the knowledge base for pediatric care and in the availability of medical products evaluated for use with children, Congress, FDA, NIH, and others have sought to create a mix of incentives and requirements to expand pediatric research and reduce barriers to the development of drugs, devices, vaccines, and other medical services that improve children's health and well-being. The next chapter describes why children's needs and characteristics warrant special attention and pose challenges to those developing, evaluating, and monitoring medical devices.

2

Medical Devices for Infants, Children, and Adolescents

"'We have to show we can make this work with the wrong equipment, and then convince someone to make us the right equipment,' Lock explained. He told me that the first device he tried to create for children was an instrument to open a stenosis, or closure, of two portals to the heart: the aortic and the mitral valves. If Lock could dilate these valves using a tiny catheter, a child with the condition could avoid open-heart surgery. He went to . . . a prominent medical-device manufacturer. The company suggested that he use a catheter designed to open a small artery in the abdomen of an adult. 'They told me there wasn't a market,' he recalled. So, for three years, Lock used the abdominal catheter to open the aortic and mitral valves of adults. This was relatively successful, and . . . [the company], convinced that there was an adult market, agreed to make an aortic-and-mitral-valve catheter—for adults. 'As an act of charity only, they made a few pediatric-shaped catheters,' Lock said. 'It's unlikely that we would ever have got the pediatric catheters built if there hadn't been an adult market—which we had to invent.'"

Jerome Groopman, 2005, p. 36[1]

This saga of medical device innovation illustrates both the special needs of children and the challenges of getting to the market a device that meets those needs. As discussed in this chapter, some medical devices may require no adaptation to be safely used with children, and some may be made smaller or otherwise successfully adapted for pediatric use. Other devices are not suitable for some or most children because, for example, they cannot be made small enough or they will interfere with or be compromised by children's growth.

Many pediatricians and other children's advocates are dismayed by the lack of satisfactory medical devices for children with certain serious medical

[1]Copyright© 2005 by Jerome Groopman. Originally appeared in the January 2005 issue of *The New Yorker*. Reprinted by permission of William Morris Agency, Inc., on behalf of the Author.

problems, and they have also expressed concern about the limited testing of device safety and effectiveness with children of different ages (AAP et al., 2004b; FDA, 2004y). These views echo those long expressed about pharmaceuticals for children (AAP, 1977, 1995). Doubtful that government or industry will invest significant resources to develop specialized devices and drugs for children, some children's hospitals have begun their own programs to do so. For example, Children's Hospital Boston has announced a Pediatric Product Development Initiative that is focusing on the initial stage of development for pediatric devices that have the potential to attract commercial investors once a promising prototype is produced (Kong, 2004).

Notwithstanding the desirability of medical devices that meet children's needs, the reality is that children are not the primary patient population for most complex medical devices. Most children living in developed countries are basically healthy. Compared to adults, especially older adults, they are far less likely to die, be hospitalized, or suffer serious illness. In the United States in 2001, people under age 20—who constitute nearly 30 percent of the population—accounted for about 2 percent of deaths and about 11 percent of hospital discharges (excluding newborns) (Arias et al., 2003; Kozak et al., 2004). In 2003, over 80 percent of children had health status reported as "excellent" or "very good" compared to about 65 percent of people aged 18 to 64 and about 39 percent of people aged 65 or over (Schiller et al., 2004).

Children are, however, overrepresented or uniquely represented among certain causes of suffering and death, notably those associated with prematurity and congenital anomalies (a diverse group of malformations, deformations, and chromosomal abnormalities present at birth). In addition, although individuals under age 20 account for about 10 percent of fatal injuries (intentional and unintentional injuries, 2001 data), they account for over one-third of nonfatal injuries (2002 data) (NCIPC, 2001, 2002).

Children, particularly newborns, are also overrepresented or uniquely represented among patients treated with certain medical devices. These devices include infant incubators, devices for closing the patent ductus arteriosus (a congenital blood vessel defect), home apnea monitors, and devices for screening hearing in newborns.

The committee found current data on medical device use by age group to be virtually nonexistent, but children clearly form a small proportion overall of patients in need of or treated with devices for serious medical conditions. One consequence is that manufacturers and others assessing the market for new, refined, or modified devices have weak incentives to focus on children's special needs and characteristics.

This chapter provides a specific pediatric context for the consideration of postmarket surveillance of medical devices used with children. It reviews definitions of pediatric subgroups (infant, child, adolescent) as well as two terms in the committee's statement of task—growth and development and

active lifestyle. It also discusses ways in which the design and use of devices have been modified (or cannot yet be successfully modified) to accommodate children's special characteristics. The concluding section describes how problems with pediatric use of medical devices may be identified: *a priori* based on a combination of expert understanding of children's developmental characteristics and detailed knowledge of the operating characteristics of a particular device; during the clinical testing of a device with children to demonstrate safety and effectiveness to the U.S. Food and Drug Administration (FDA); and as experience with a device accumulates following its entry into the market.

DEFINITIONS

Infant, Child, Adolescent

As described in Chapter 1, this report generally uses the term *children* broadly to include all pediatric age groups. Definitions vary for the subgroups infant, child, and adolescent and tend to reflect the concerns and purposes of those developing them. The definitions serve primarily as general guides that encourage attention by clinicians, researchers, policymakers, and others to developmental differences—physical, cognitive, and psychological—within young populations and between younger and older populations.

In guidance documents on pediatric drug testing and assessment of pediatric medical devices, the FDA has defined *infants* as those younger than 2 years of age (FDA, 1994, 2004p; ICH, 2000).[2] The discussion of drug testing notes that this is a period of rapid development in the central nervous system, immune system, renal and hepatic pathways of drug clearance, and body size. While this development is underway, products that are reasonably safe for adults and even older children may be riskier, even lethal, for babies. (An example is verapamil, an antiarrhythmic medication that should be avoided in the young infant.)

The guidance for medical devices does not single out infancy as a period of particular vulnerability, although instances of vulnerability can be cited. For example, studies have repeatedly found infection rates for implanted cerebrospinal fluid shunts to be higher in premature neonates than in other children (see, e.g., McGirt et al., 2003). With respect to certain medical procedures, however, infancy may be a preferred time for interven-

[2]In contrast to FDA, the Centers for Disease Control and Prevention (CDC) defines infant as someone in the period from birth through the first year of life (age 0 to <1 year of age). The CDC definition reflects the agency's particular interest in data to guide policies and programs to reduce infant mortality. Children under age 1 account for half of all deaths among those under age 20 (Arias et al., 2003).

tion because of the infant brain's particular plasticity, that is, its ability to mold or shape itself to accommodate to damage in one area with new growth and connections to other areas to achieve the same function (Johnston et al., 2001; Luciana, 2003). Studies of long-term outcomes are still important to determine whether such accommodation compromises other neurodevelopmental processes as the child matures.

Although the wording is slightly different in documents on drugs and devices, a child is regarded as an individual between the ages of 2 and 11 (FDA, 1994, unpaged; ICH, 2000; FDA, 2004p). For certain conditions and medical products, differences within this age group in cognitive and emotional development may be significant, particularly with respect to the use of medical devices that normally require user set-up steps, user programming, or other patient-initiated control. What is well beyond the capabilities of a 3-year-old may be quite manageable for a 10-year-old. Physiologic differences within the 2-to-11 age group also may be important. For example, younger children whose bones heal more quickly may be safely treated for femoral fractures using a body cast, whereas children aged 6 to 12, who heal more slowly, may benefit from surgical treatment that requires a shorter period of incapacitation (see discussion of titanium nails below).

For drugs and devices, FDA documents differ on the age range for *adolescents*. For drugs, the range is ages 12 to 15 ("up to age 16") (FDA, 1994, unpaged). For medical devices, however, the upper end of the range is age 20 (or "up to the age of 21") (FDA, 2004p, p. 4). In specifying this broader range, the guidance on medical devices states: "Given the scope of medical devices and the impact that a device could have on a growing adolescent, as well as the effect growth could have on the device, we believe that including the upper age limit identified above may be useful for some devices and device clinical trials" (FDA, 2004p, p. 4). No specific instances are cited. The guidance also notes that "the descriptions are somewhat arbitrary and that, in fact, the subject's weight, body size, physiological development, neurological development, and neuromuscular coordination may often be more appropriate indicators than chronological age" (FDA, 2004p, pp. 4–5).[3]

[3]The National Institutes of Health (NIH) policy statement on the inclusion of children in research also applies to "individuals under the age of 21 years" (NIH, 1998, unpaged). NIH requires research proposals to describe the rationale for including or excluding particular age groups in studies. The statement notes that the definition differs from the regulations of the Department of Health and Human Services governing children's participation in federally conducted, supported, or regulated research. Under these regulations, state law on the age of majority governs decisions about whether the regulations apply, and nearly all states specify age 18 as the age of majority. Under NIH policy, an 18-year-old would be an adult for consent purposes (under state law) but a child for study inclusion purposes. The policy statement was developed in response to language in House and Senate Appropriations Committee reports for fiscal year 1996 that noted the need for the more widespread inclusion of children in research (NIH, 1998).

Growth and Development

From infancy through adolescence, children mature physically, cognitively, and emotionally. Pediatrics as a medical specialty arose out of recognition that the care of children should be informed by knowledge of how children's growth and development may affect and be affected by clinical care. One question for this report, as examined in Chapter 6, was whether postmarket surveillance studies continue long enough to evaluate the effects of growth and development on the longevity of implanted devices.

Growth in size is one of the most obvious aspects of the human passage from birth to adulthood. As discussed further below, some implants have limited or suboptimal pediatric applications because they cannot grow as the child grows or they interfere with growth. Many implants (e.g., artificial blood vessels [synthetic conduits]) can be replaced with larger sizes as a child grows, but repetitive surgery for this purpose presents risks, including difficulties related to dissection through accumulated scar tissue. Children's growth and development may dictate a more frequent monitoring schedule than is necessary with adults.

Growth can also shift the location of an implanted device, for example, when an implant fixed to bone migrates to an undesired place as the bone grows. One goal for innovation in biotechnology is to devise materials and processes that allow implants to grow with a child or work in ways that do not interfere with growth.

In addition to physical growth and size, other *developmental* differences or changes may be relevant to medical product use. For example, as children develop, they not only get larger but also gain in strength, dexterity, and gross and fine motor skills (Pena et al., 2004). These gains may be necessary before they can independently operate certain devices such as patient-operated drug infusion or electrical stimulation systems.

Metabolic, hormonal, and other developmental differences may be relevant for some implanted and other devices (e.g., cardiopulmonary bypass machines) that come into contact with a child's tissues. Questions have, for example, been raised about the long-term consequences of extensive infant exposure to a chemical used in making plastic for the tubing employed in an array of devices for neonatal intensive care (Rais-Bahrami et al., 2004).

To cite yet another kind of developmental consideration, clinicians and researchers have identified tactile, visual, and auditory overstimulation as a concern for ill infants who depend on ventilators and other medical devices to assist their breathing, nutrition, and other functions (ATS, 2003). Guidelines for clinicians have suggested modifications in the setting and use of treatments to minimize such stress.

Cognitive and psychosocial development and social environments are relevant to the safe pediatric use of certain medical devices, particularly

complex devices used outside the hospital. For chronically ill children reliant on medical devices, psychological and intellectual development (assuming their condition permits it) includes learning how to manage the devices independently and safely. For example, older children who have a tracheostomy can learn to manage a device that permits them to talk with the tracheostomy tube in place.

Sometimes psychosocial development brings risks. For example, older adolescents may be less receptive than children and younger adolescents to parental monitoring of adherence to practices necessary for safe and effective device use. In a similar vein, a clinician in a large pediatric diabetes center has written that "[t]eens are probably the least reliable group to start on the [insulin infusion] pump" because they easily learn to use it but "are typically preoccupied with many other things, and the pump quickly goes down on the priority list" (Ahern, 2001, unpaged).

Risk-taking behavior by adolescents is, generally, a long-standing public health concern (see, e.g., Rolison and Scherman, 2002; Kelley et al., 2004; Steinberg, 2004). Some recent research suggests that the areas of the brain that limit such behavior may not fully mature until a person reaches the mid-twenties (Giedd, 2004).

Finally, one consequence of children's developmental characteristics is that children often depend on their parents or other adults to provide their medical history to clinicians and to answer and ask questions about a medical problem or its care. Many survey-based measures of pediatric health care quality and outcomes have different forms for children of different ages, and those involving younger children often direct questions at parents (see, e.g., Hermida et al., 1999; Bradlyn et al., 2003; Beal et al., 2004).

Children's Active Lifestyles

> *"It has been quite a while since I have had a [hydrocephalus shunt] revision. . . . There was a period in time when I had five or six in a row, just back to back. The main reason for that [was that] I was racing wheelchair competitively, at the national level, for a while. . . . The shunt really couldn't keep up with the strenuous activity. It couldn't drain the fluid off my brain fast enough. . . . Eventually, we found a valve that would drain the fluid quick enough."*
>
> Ben Harder, 2004

Another question considered in this report is whether postmarket surveillance studies are adequate to evaluate how children's active lifestyles may affect failure rates and longevity for implanted devices (see Chapter 6). Although the term *active lifestyle* may convey an image of a child in motion

with the potential for colliding with other beings or objects, it has no common clinical or behavioral definition.

The committee interprets children's active lifestyles as having physical, cognitive, emotional, behavioral, and social aspects that are affected by a child's stage of development. Physical aspects relevant to device safety include the types of activities engaged in by children of different ages, the environments in which they occur, and their frequency, duration, and intensity.

When FDA granted a humanitarian device exemption for use of a deep brain stimulator with dystonia patients who are 7 years of age or older, it noted that children's active play and sports participation could damage elements of the implant. It went on to say that "[w]hile some degree of rough play may be unavoidable, children should be advised to avoid games, sports and other pastimes where a strain to the lead/connector assembly or a percussive injury to system components may be likely to occur (e.g., soccer, football/rugby)" (H020007, FDA, 2003, p. 3). (Chronic intractable dystonia is a serious neurological condition characterized by involuntary muscle spasms and abnormal postures or movements.)

The developmental control that children can exert over their physical activity is also relevant to device safety. For example, an infant in a crib and a cognitively intact 14-year-old confined to bed due to illness or injury may both be relatively inactive. The adolescent can, however, be expected to have more awareness of and control over movements such as rolling over that might dislodge or otherwise impair the functioning of a medical device such as a catheter or a breathing tube. Likewise, a 5-year-old and a 25-year-old who have had a cardiac pacemaker implanted may each know that they need to protect the device, but developmental differences in the understanding of risk and causation and in the control of impulses increase the probability of risky behavior by the child, for example, jumping off a porch (see, e.g., Giedd, 2004).

Surgeons may modify their procedures to take children's activity levels into account. For example, surgeons who perform craniofacial surgery that requires a tracheal or breathing tube may secure the tube by placing wire sutures through the gum because of the high risk of having this tube inadvertently dislodged by the movement of a child and the extreme difficulty of replacing the tube when the facial structures are swollen.

Surgeons implanting a pacemaker in a very young child often will place the pacemaker generator in the abdominal wall, where extra tissue provides more protection than is offered by the usual location near the collarbone. With the usual location, the surgeon connects the generator to the inside of the heart by passing the pacemaker's leads (small wires) through a vein in the chest. With abdominal placement, surgeons tunnel

the leads through the chest tissue and then stitch them to the outside of the heart. This approach allows the surgeons to avoid placing the leads through young children's small subclavian veins, where they might cause a thrombosis that would complicate access for pacemaker leads in future years if needed, for example, as the child grows or if problems arise with the original leads.

The social dimensions of children's lifestyles, especially adolescent lifestyles, are sometimes featured in discussions of medical devices such as insulin pumps and catheters for peritoneal dialysis that require special attention while users are away from home. Websites for children and teens with diabetes provide tips for living with the insulin pump and include discussion of clothing, eating, school physical education activities, and swimming and other sports.

In addition, as the committee heard during its meeting with families, the desire to be or appear "normal" may cause older children and adolescents—with mixed emotions and reactions from their parents—to engage in activities (e.g., playing contact sports while having an implanted pacemaker) that place great stress on implanted or partly implanted devices such as catheters. Some complications associated with pediatric use of medical devices may result from patient activities that have a realistic potential for harm, given the inherent limitations or characteristics of the device. A continuing interest of clinicians, parents, and device manufacturers is strategies for "child-proofing" devices by changing their design or use.

For infants and toddlers, the use of medical devices may also need to take into account another "lifestyle" factor—their lifting, holding, carrying, and other handling by adults. Just as special precautions may be needed to safely secure a device for infant or child activity, so additional precautions may need to be taken with medical devices to accommodate normal child care.

Yet another consideration is that children living at home with complex medical devices often have siblings whose own "active lifestyle" may create safety issues. On the one hand, siblings could endanger an ill brother or sister through play that dislodges or otherwise interferes with a device. On the other hand, playful or curious siblings could encounter electrical and other hazards to themselves. For example, children have electrocuted themselves after inserting partially or completely disconnected electrode wires from a sibling's cardiorespiratory monitor into wall outlets (Katcher et al., 1986). Family education and parental monitoring are essential safeguards, but thoughtful design or choice of device that considers home environment and other "human factors" also has a role to play in protecting the safety of all members of a family.

FDA GUIDANCE ON ASSESSMENT OF PEDIATRIC MEDICAL DEVICES

As required by the Medical Device User Fee and Modernization Act of 2002 (P.L. 107–250), FDA recently provided guidance on the premarket assessment of pediatric medical devices. The guidance includes a general discussion of developmental considerations and lists a number of factors that should be considered in designing devices or planning clinical studies of devices (FDA, 2004p). The listed factors, which are not mutually exclusive or exhaustive, are

- height and weight;
- growth and development;
- disease or condition;
- hormonal influences;
- anatomical and physiological differences from the adult population;
- activity and maturity level; and
- immune status.

In a further discussion of "unique host characteristics" of pediatric patients, the guidance offers some illustrations of how these characteristics might figure in the assessment of a medical device. For example, in recommending that assessments consider stage of puberty and other developmental milestones, the guidance suggests that clinicians should consider breast bud development in the placement of certain medical devices in infant or young girls (e.g., placement of chest tube in a tiny infant to relieve air or fluid that has collected in the chest, but outside the lungs).

The guidance also summarized the circumstances when clinical data for pediatric populations are appropriate. These circumstances are when

- supporting information from sources, such as preclinical bench or animal testing, literature, or adult clinical trials, are inadequate to establish safety and effectiveness for the pediatric indication;
- adult data are inadequate to predict pediatric risks and adverse events;
- pediatric data are needed for validation of design modifications; or
- pediatric data are needed to develop an age-appropriate treatment regimen.

Specific testing requirements will vary depending on the device. FDA, however, stated that its expectations for such tests generally involve the same basic questions and procedures for both adult and pediatric populations.

An article by FDA staff includes additional discussion of pediatric factors as they relate to neurological devices (Pena et al., 2004). With respect

to surgical risks, for example, the authors cite concerns about blood loss for patients with small volumes of blood, possible need for sedation for children who cannot control movement during procedures, and repeat surgeries associated with device replacement or growth-associated migration of a device. They note that of 19 high-risk medical devices involving the central and peripheral nervous system that FDA approved between 1994 and 2003, 8 included indications for use in children as well as adults.

In addition to the guidance on premarket assessment, the agency issued guidance on procedures to ensure that advisory panels that review documents such as applications for premarket approval of medical devices appropriately include or consult with pediatric experts. This guidance, which responds to another provision in the Medical Device User Fee and Modernization Act (21 USC 360(e)(c)), provides for pediatric expertise to be available (through consultation or inclusion in panel deliberations) in a range of situations. These include when

- there are labeled indications for use that include a pediatric subpopulation or there is a reasonable likelihood that the device would be used in a pediatric subpopulation for the labeled indication;
- there are data in the study that include a pediatric subpopulation;
- there is a reasonable likelihood that the data from the study in the adult population may be used by the applicant to subsequently support a pediatric indication;
- there is a need for advisory panel input on a study design and/or protocol for use of the device in the pediatric population; or
- there is a reasonable likelihood that the advisory panel may discuss the potential use of the device in the pediatric population.

The next section of this chapter considers how children's special needs and characteristics may be taken into account in the design and use of medical devices. The descriptive categorizations reflect the committee's experience and perspectives, reviews of the literature, and information provided during public meetings and other discussions with experts.

DEVICE DESIGN, DEVICE USE, AND DEVELOPMENTAL DIFFERENCES

Children are not small adults—a cliché but true. As described above, children, especially infants and young children, differ from adults in ways that extend beyond the obvious difference in size. These differences may have implications for the design and use of devices and for the methods to evaluate their safety and effectiveness before and after marketing.

Developmental differences between children and adults related to the safe and effective use of medical products have been most extensively analyzed and described for drugs.[4] For drugs, scientists and clinicians have constructed a strong rationale for pediatric drug research to assure the safe and effective use of medications with children (see, e.g., Shirkey, 1968; AAP, 1995; Kearns and Winter, 2003; IOM, 2000b, 2004a; Reed and Gal, 2004). Data indicating that some 80 percent of medications listed in the *Physician's Desk Reference* lacked any prescribing information for children have also been cited to build the case for such research (AAP, 1995; Steinbrook, 2002).

For medical devices, the committee found nothing equivalent to the pharmacology literature on developmental concerns. With drugs, one is generally considering issues along a spectrum: ingestion, bioavailability, action, untoward actions, metabolism, and disposal of metabolites. This is complex enough. With devices, one might be considering physical interactions (e.g., when a device exerts pressure on skin), metabolic interactions (if a device or component is not inert), and growth (if a device is implanted or connected with a child over an extended period), among other factors. Box 2.1 summarizes some of the developmental considerations for drugs compared to medical devices.

To the extent that pediatric considerations are known for a medical device, the labeling of the device should reflect that knowledge. In some cases, labeling will state that use of a device is not indicated in those under a certain age or those who are not skeletally mature. In other cases, the labeling may describe adaptations or cautions related to pediatric use (see, e.g., the discussion earlier of the deep brain stimulator).

Spectrum of Medical Device Use with Children

The use of medical devices with children spans a wide spectrum, including devices that are used uniquely with children, devices that are reduced in size or otherwise modified for use with children, and devices that do not differ for adult and pediatric use (although some procedures for their use may vary). Use with children is explicitly precluded for some devices.

Box 2.2 and the following discussion illustrate the spectrum of pediatric device use. The use of particular devices as examples does not necessarily imply a committee judgment that the devices have been adequately studied for short- or long-term safety or effectiveness in use with children.

[4]A major field of pharmaceutical science and testing relevant to development changes involves pharmacokinetics, which relates to the ways medicines are absorbed, metabolized, and otherwise processed in the body and the relationship between drug doses and the concentration of medicines in the blood. Developmental changes can also affect the drug receptors that mediate how medicines act in the body, that is, their pharmacodynamics.

BOX 2.1
Examples of Developmental Considerations or Potential Complications for Drugs and Devices

Drugs
- Dosage often related to weight or other body size index
- Formulations (e.g., liquids, capsules) suitable for different ages
- Developmental differences related to absorption route (e.g., through skin, in gut)
- Bioavailability
- Development differences in metabolism and excretion of drugs
- Potential to cause tumors or genetic mutations
- Drug–drug interactions

Devices
- Device choice often related to child's size
- Compatibility of device with growth
- Durability (e.g., resistance to material fatigue and failure related to children's activities)
- Site stability (e.g., protection against dislodgement, migration, or perforation)
- Biocompatibility of materials with tissue in children of different ages
- Pressure on tissue
- Infection hazards (e.g., passage of a device through skin or colonization of device surface by antibiotic-resistant biofilm)
- Electrical or radiation hazards

Devices Unique or Nearly Unique to Children

Sometimes children, especially infants, have unique needs or conditions for which specialized devices are developed. The infant incubator is an obvious example.

In addition, children may so dominate the target population in need of a device that the consideration of adult users is secondary rather than primary. One example of a device initially developed for children is the atrial septal occluder. It was originally intended to treat children who have a hole in the wall separating the inflow chambers of the left and right sides of the heart, but it has also been used to treat adults with that condition (Omeish and Hijazi, 2001; Thomson et al., 2002). To cite another example, FDA recently granted limited approval (through a Humanitarian Device Exemption, as discussed in Chapter 4) for a pulmonary valved conduit (a kind of heart valve) that is, again, primarily intended to correct congenital heart defects in children but can be used with adults (H020003, FDA, 2003a). (Although congenital heart disease is sometimes regarded as a condition of children, estimates suggest that there are at least as many adults living with congenital heart disease as there are children [Warnes et al., 2001; Hoffman et al., 2004]).

BOX 2.2
Design or Adaptation of Medical Devices for Use with Children

Devices unique to children
- Infant caps
- Nursing bottle nipples
- Infant incubators
- Cranial orthosis (helmet to correct cranial asymmetry in infants)
- Bililights (lights used for treatment of neonatal jaundice)
- Newborn hearing screener

Devices developed primarily for children but also used with adults
- Atrial septal defect occluder
- Cerebrospinal fluid shunt

Same core device, different accessories for pediatric use
- Pulse oximeter with different sensor attachment for infants
- Automated external defibrillator with paddles that deliver attenuated charge based on pediatric-specific algorithms

Variations in device use or technique to accommodate developmental differences
- Adjustment in radiation dose and frequency for computed tomography
- Shift in implantation site for pacemakers used with young children
- Use in pediatric cardiac procedures of adult bile duct stents

Devices that vary in size for use with small patients
- Baclofen infusion pump
- Bronchoscopes
- Heart valves
- Testicular prosthesis
- Intravenous catheters and needles

Same Device for All Patients

Sometimes the same monitoring, diagnostic, or therapeutic medical device is used for adults and all or most children without requiring pediatric modifications in size, design, or key accessories. For example, ear thermometers do not vary in size for adults and children nor do syringes, although needle sizes vary. Nonetheless, even when devices are identical or very similar, clinical care of children may still differ from care of adults in general ways, for example, by involving physicians, nurses, and others experienced in pediatric care and by providing physical settings that are "child friendly."

In some cases, adaptations in devices or accessories have followed the identification of adverse outcomes in children. For example, the same size tubing was initially used for all mechanically ventilated patients to connect

the ventilators to the tracheal tube, but the heavy weight of the tubing created problems for infants and children because the tubing tugged on the breathing tube, making it more likely to dislodge. This led to the use of child-appropriate tubing. To cite another example, when problems arose in the use with young children of adult ventilators that had high gas flow rates, companies developed ventilators that provide smaller breaths of air and a slower gas flow rate.

Some innovations—notably, successful miniaturization of device components—may allow a move away from devices made in different sizes toward "one-size-fits-all (or most)" devices. For example, a new left ventricular assist device that is intended to reduce the size and weight of first-generation devices was aimed primarily at adults but the size also allows use with children. (In 2004, FDA approved a humanitarian device exemption for this device for use with children aged 5 to 16 years—before the device was approved for use with adults [H030003, FDA, 2004a].)

Same Core Device, Different Accessories

For some technologies, the core medical device may be the same, but the accessory devices that connect the patient to the device may differ based on patient size or other characteristics. Thus, a dialysis machine can be used for adults and children if the tubing and dialysis coils are reduced in size for small patients. Similarly, a basic pulse oximetry monitor can be used with all age groups, but the sensors that attach the device to the patient vary in size. The sensors may also be attached differently for very young patients (e.g., attached with a gentler adhesive to avoid damaging an infant's fragile skin or cuffed around an infant's wrist or ankle rather than attached to a finger).

Another example of a core device with a different accessory for children is the automated external defibrillator for use by first responders outside the hospital. In 2001, FDA approved an external defibrillator for use with children under age 8 (FDA, 2001e). It comes with two sizes of defibrillator pads (which are placed on the chest to deliver the electrical shock). The smaller pads for children attenuate or reduce the shock delivered. The firm that developed the device also collected pediatric heart rhythm information to create new algorithms that determine when a shock is appropriate for a child (Acute Care, no date; Cecchin et al., 2001).[5] In

[5]Given the lack until recently of pediatric data on which to base automated assessments of whether a shock was appropriate and concerns about whether children's differing physiology warranted attenuation in the electric shock delivered, children were characterized as "'orphans' with respect to this effective technology" (Samson et al., 2003, p. 3251).

2001, the device was cleared for marketing without testing in children (K003819, FDA, 2001). The sponsor, however, voluntarily agreed to study 50 children for which the device was deployed to gather data on use and results in actual emergency care practice (personal communication, Thomas P. Gross, M.D., Director, Division of Postmarket Surveillance, CDRH, November 7, 2004).

Same Core Device, Adaptations in Programming, Placement, or Operation

When a device does not vary by size of patient, safe and effective applications with children may require other differences or adaptations. Such adaptations may involve changes in the clinical indications for use of a device, the frequency or duration of use for the same indication, the way an implant or its connections are sited in the body, the surgical method used for implantation, or the programming of automated operations such as alarms based on abnormal physiologic signs. For example, many heart rate monitors are used for adults and children, but the alarm settings are adjusted based on the normal range of heart rate for different age groups. As mentioned in the preceding section, the automated external defibrillator approved for use with children under age 8 uses different algorithms for children and adults to determine whether a shock is indicated.

For the deep brain stimulation device described earlier, FDA notes that if two stimulators are used with small patients, their physical placement may need to deviate from that normally used for adults to establish enough separation to minimize electromagnetic interference. For smaller patients, the manufacturer suggests placing one neurostimulator in the abdomen and one in the chest region.[6] (See Vidailhet et al., 2005, for a description of a controlled [nonrandomized] prospective study of the device and Greene, 2005, for a commentary on the need for more data, including data on long-term outcomes.)

A different rationale for modifications in device placement applies for central vascular catheters. With infants, it is difficult to identify the physical

[6]For pediatric patients, the FDA approval order suggests evaluating "the patient's implanted lead/extension assembly for sufficient strain relief (e.g., consider patient comfort, range of motion, X-ray visualization of the extension) at regular post-implant follow-up sessions, especially for patients whose growth is not complete at implant" and considering "replacement of the extension with one of greater length during other elective surgery procedures, such as during the regular change out of neurostimulators that must occur because of battery depletion" (H020007, FDA, 2003, p. 2). In addition, the manufacturer suggests that the device be used with people whose brain growth is 90 percent complete to reduce strain on the leads as the child grows.

landmarks for placing the catheter in the neck (jugular vein) or the upper chest (subclavian vein), and safe placement may require considerable sedation. Therefore, the groin is often selected because landmarks for placement of the catheter can be readily identified and the site can be well anesthetized with less risk of excessive sedation. At the same time, constant moisture, repetitive movement, and other factors make it more difficult to maintain a sterile insertion site in the area. One consequence is that infants with the device tend to show higher rates of infection than adults.

For computer-assisted tomography (CT), several kinds of adaptations have been proposed based on children's greater vulnerability to the damaging effects of radiation and an increasing recognition that CT scans can deliver significant radiation to children (see, e.g., NRC, 1990; NCI and SPR, 2002). Underscoring the importance of long-term evaluation of medical devices and associated procedures, FDA, the National Cancer Institute, and others have issued guidelines to minimize the harmful effects of repeated diagnostic CT scans on children (Feigal, 2001b; NCI and SPR, 2002; see also Frush and Donnelly, 2001; Frush, 2003). They advise clinicians to

- take advantage of equipment advances that allow more sensitive dose management;
- develop and use charts or tables to guide equipment settings based on patient weight or diameter and body area to be scanned;
- limit repeat scans to what is essential;
- scan the smallest area of the body possible; and
- scan at the lowest dose of radiation and lowest level of resolution necessary to achieve needed image quality.

Adjustments in Device Size

Sometimes the physical size of a medical device is the main issue with pediatric use. Infant or child versions exist for many common medical devices such as hospital beds, bandages, and scales.

More complex devices can often be manufactured in sizes to fit all or most pediatric uses without compromising their structure or function. For example, leads for implanted cardiac pacemakers used with children can be made shorter than adult leads without compromising their function, although surgical implantation techniques may vary, especially with infants. To cite another example, a saline-filled testicular prosthetic implant that has been tested in adults and children with a congenitally absent or surgically removed testicle is now available in an extra small size (P020003, FDA, 2002). For this and other implanted devices, replacement with a larger size may be anticipated to accommodate a child's growth.

Intraocular lens replacement, which has long benefited adults suffering from cataracts, can also help children with certain vision problems. The sizes of the replacement lenses developed for adults are not, however, appropriate for young children. (The mean axial length of a newborn's eye is 17 mm, whereas that of an adult is 23 to 24 mm.) In addition, the surgical procedure must accommodate developmental considerations such as lower scleral rigidity, greater elasticity of the anterior capsule, and higher vitreous pressure (see, e.g., Dahan, 2000; Ahmadieh and Javadi, 2001; Good, 2001; Pandey et al., 2001).

For certain implanted devices, reductions in size have brought benefits to both children and adults. The cardiac pacemaker is a notable example. Figure 2.1 and Figure 2.2 show the difference in size between an external pacemaker (circa 1957) that was designed to provide short-term life support and a recent implantable pacemaker that offers long-term support.

In some cases, sizing of a device is done at the time of use. For example, cardiac shunts or tubes that are used to connect two blood vessels come in

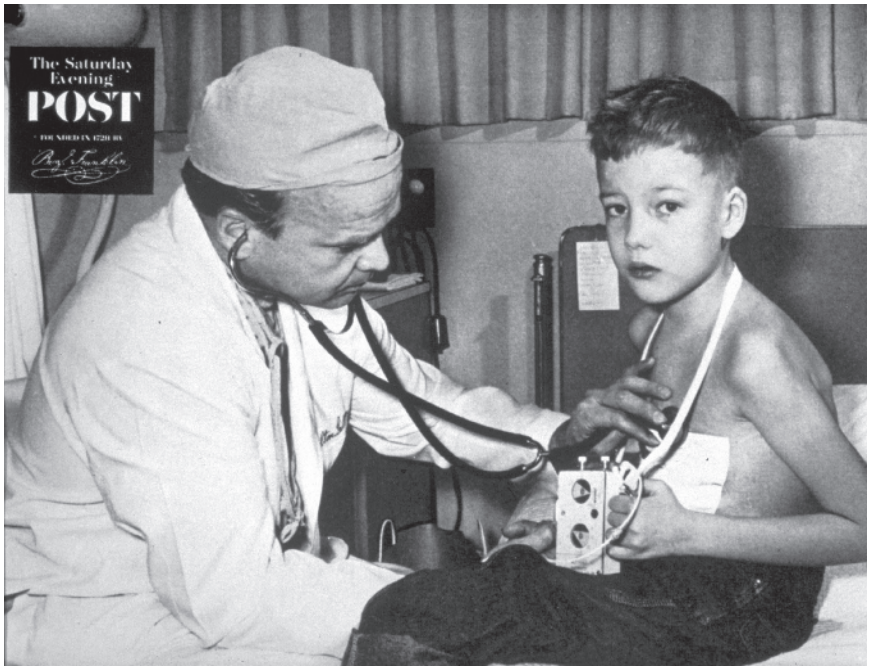


FIGURE 2.1 Child with early external pacemaker, c. 1957 (Used with permission of *The Saturday Evening Post*).

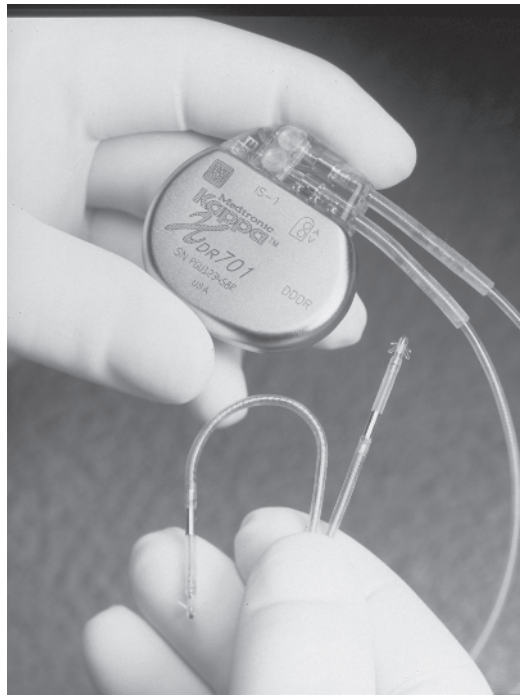


FIGURE 2.2 A modern implantable pacemaker (Medtronic Kappa® 700 series) (Reproduced with permission of Medtronic, Inc.).

different diameters. The appropriate length is determined by the surgeon who cuts them to size just before insertion.

Size adjustments may not be straightforward, even for relatively simple devices. A case in point involves tracheostomy tubes, which are adjusted to fit different size windpipes by creating an array of sizes that vary by increments of 0.5 mm in diameter and simultaneously differ in length. In a child with an abnormally narrow airway, the tube with the appropriate diameter may be too short, which can cause it to become dislodged. Specially constructed tubes can be ordered from the manufacturer, but this option is not feasible in an emergency situation.

Lack of a device in sizes appropriate for the full range of pediatric patients may limit the use of certain interventions. For example, in intracardiac echocardiography (an imaging technique used to guide certain cardiac procedures), the size of the catheter used in the procedure has limited use with very young patients. (The technique, which has not been fully tested in randomized clinical trials, avoids an imaging procedure that requires intu-

bation and general anesthesia [Alboliras and Hijazi, 2004; Zanchetta and Maiolino, 2004].)

Limits to Downsizing or Other Adaptations

Reducing the size of a device that is too large for some or most children may not produce desired results. The reasons may relate to mechanical properties of the device or to characteristics of children other than size. For example, with certain kinds of devices through which blood moves, changes in fluid dynamics in small spaces must be considered. Efforts to shrink left ventricular assist devices (which have been used to support patients awaiting heart transplants) have encountered problems because "blood flow in the smaller version is completely different than in the larger adult heart devices. . . . [D]ead zones, or low-rate flow zones, can form inside the blood pumps . . . [and] slow-flowing blood can create clots" (PSU, 2004, unpaged). The miniaturized device mentioned earlier in this chapter, which was not developed specifically for the pediatric population, is designed to minimize such disruptions in blood flow (Bluck and Petty, 2000).

As described above, tracheal tubes are manufactured in different sizes to accommodate the range of airway dimensions of infants, children, and adults, but problems may arise with very small sizes. Although an appropriately sized tube exists to fit in the small airway of the premature infant, the thin wall of the tube has a propensity to kink or buckle, which can cause the tube to become obstructed. Caregivers have developed various means to limit these problems by stabilizing the tube externally (e.g., by wrapping it with tape or taping it to a tongue blade). Also, smaller tubes also are more easily obstructed with mucus and need to be cleared frequently. With a small tube, a small suction catheter is needed, and these small catheters are flimsy and more difficult to use than the larger, thicker suction catheters.

Different limitations arise with mechanical ventilators that are equipped with triggering devices that sense effort by the patient to breathe, which then causes the ventilator to provide a breath. Such triggering devices have not been sensitive enough to detect inspiratory effort in very small babies. Hence, other types of devices, such as a kind of capsule on the chest, have been developed to try to coordinate the effort of the patient and the response of the ventilator.

For sick infants requiring mechanical ventilation, an additional concern is the lack of acceptable face masks. Masks can be made small enough to fit infants, but the pressure needed to create a tight fit and avoid air leakage can bruise or abrade fragile infant skin. Other respiratory devices such as nasal prongs may need to be monitored closely to prevent skin damage and necrosis when used with infants. More generally, the thinness and other

characteristics of children's skin, especially infant's, can require care with or modifications of devices that touch the skin to reduce the potential for bruising or skin damage associated with heat, pressure, friction, or other processes.

Skin thickness may also be an issue with certain implants. In a report of pacemaker failures associated with twiddler's syndrome (when patients deliberately or subconsciously spin the pacemaker's pulse generator, which can dislodge and damage the pacemaker leads), the authors noted that children might be more susceptible to the problem "because they have thinner subcutaneous tissues, making leads more accessible, and their comprehension of the consequences may be poor" (Abrams and Peart, 1995, p. 190).

Devices That Accommodate Children's Growth

A unique pediatric problem with the use of certain implanted medical devices is that they either interfere with growth or do not grow as children grow. The approved labeling for a number of orthopedic and other implants describes them as not indicated for individuals with growing bones or skeletal, skull, or other aspect of growth that is less than 90 percent of adult levels (see, e.g., H010002, FDA, 2001; P000057, FDA, 2001; P000058, FDA, 2002; P000013, FDA, 2003).

Some devices or their accessories or the procedures for their use are designed to take children's growth into account. For example, when surgeons first began to insert the drainage catheter for cerebrospinal fluid shunts into the abdomen, they used tubing just long enough to enter the peritoneal cavity. As children grew these catheters had to be replaced with longer ones. Recent experience suggests that even infants can tolerate a peritoneal catheter long enough to accommodate growth to adulthood (Couldwell et al., 1996). Cardiac pacemaker leads are also implanted so that some significant amount of growth can be accommodated.

Given the risk and discomfort of replacing an implant as a child grows and given the restrictions on the use of certain devices that interfere with (or are compromised by) growth, implants that can "grow" with a child have obvious appeal. Growing children who have bone cancers removed from their limbs and prosthetic devices inserted have faced repeated surgeries to replace or expand the device to accommodate growth. FDA recently approved a device that can be expanded without surgical intervention. As described by FDA, the device employs "a coil that fits around the patient's leg that produces an electromagnetic field (EMF). The EMF induces an electrical current and subsequent heating of an internal wire [in the implant]. The generated heat softens a polymer locking ring, allowing a slow expansion of an internal compressed spring. The spring expansion pushes the spring housing and femoral housing apart, thus increasing the overall length of the

implant" (FDA, 2003p, unpaged; see also K021489, FDA, 2002). According to the manufacturer's webpage, FDA has cleared the device for distal femur and proximal tibia implants, but implants for the humerus, proximal femur, and total femur are only available so far under compassionate use guidelines (see Chapter 4) (Wright Medical Technology, Inc., 2004).

To cite another orthopedic example, pediatric orthopedists treating children with leg fractures have increasingly used flexible titanium nails that support the leg as the bone heals but also provide flexibility for growing bones. For children between the ages of approximately 6 and 12, the technique avoids some of the disadvantages of alternative treatments with either a body cast and traction or certain rigid nailing techniques (ECRI, 2004a; Flynn et al, 2004). This technique has not been associated with problems of arrested growth in the trochanter (part of the femur) or osteonecrosis of the head of the femur that have sometimes been reported with rigid nailing techniques (see, e.g., Townsend and Hoffinger, 2000; Alonso and Slongo, 2001; Bartholomew et al., 2001).

Interest in another kind of device, the resorbable implant, is particularly strong among those who treat children with certain craniofacial and orthopedic deformities. These implants are adequately rigid to support repair or reconstruction of a deformity for several months, but they then disappear without requiring removal or replacement and without appreciably interfering with a child's growth. In a statement to the committee, the American Academy of Pediatrics (AAP) pointed to metal craniofacial fixation devices that create problems with children that are not seen in adults. AAP cited "thinning of scalp leading to annoying prominence of the device . . . subcutaneous migration of screws . . . [and] intracranial migration of the devices" (AAP et al., 2004b, p. 8). In the latter process, the device has been engulfed by the child's growing skull such that "within a few years plates and screws were sometimes found inside the dura resting in the substance of the brain," a location for which they clearly were not intended.

Until recently, only the results of short-term studies of resorbable implants were available, but investigators have now reported on a combined prospective and retrospective multisite analysis of nearly 2,000 patients under 2 years of age treated over a 5-year period with the same type of device (see, e.g., Eppley et al., 2004). They found a lower rate of device-related complications requiring reoperation than for metal devices and low rates of adverse events (e.g., infections, instability, and foreign-body reaction). Consistent with a characteristic of device innovation, they noted that "the specific types of plates and screws used evolved over the study period from simple plates, meshes, and threaded screws to application-specific plates and threadless push screws whose use varied among the involved surgeons" (Eppley et al., 2004, p. 850).

In an arena that holds potentially broad promise, the emerging field of

tissue engineering is exploring the development of devices such as heart valves or skin that become populated by the patient's living cells (see, e.g., Rabkin et al., 2002; Stock et al., 2002; Mol et al., 2004; Neuenschwander and Hoerstrup, 2004). Such devices might grow as young patients grow and also avoid or limit immunocompatibility or biocompatibility problems that are often seen with currently used materials.

Other Developmental Concerns

The use with children of implanted heart valves that employ tissue from pigs or cows raises a variety of developmental considerations. When surgeons began implanting such valves in children, they discovered in the course of long-term follow up a more intense immunologic response and more rapid calcification of the valves than had been observed in adults or expected with children (see, e.g., Geha et al., 1979; Schaff and Danielson, 1986; Baskett et al., 2003). The valves, which avoid the risks associated with the anticoagulant therapy required for mechanical heart valves, are still occasionally used with children—with the now familiar risk of calcification factored into decisions about which treatment is best for a particular child.

As noted above, some medical devices that are critically important for certain conditions require cooperation from the patient that may not be possible for infants and very young children. The options in such situations may involve adaptations in the device, development of an alternative device, or foregoing use of the device until the child has matured.

The last two options are both in evidence for patients with cystic fibrosis. Measuring lung function in these patients requires that the patient be capable of certain breathing maneuvers (e.g., taking or expelling a breath upon direction). For infants to age 2, a system has been developed that includes, among other features, a vest that inflates to provide external pressure for the required breathing maneuver (Tillman, 2002). For children between ages 2 and about 6, no satisfactory device has yet been approved (Colin, 2003).

With some devices and therapies, multiple factors, including behavioral factors, may be at work. For example, the design and use of aerosol delivery devices for young patients who have cystic fibrosis and certain other respiratory disorders may be complicated for a combination of reasons, including anatomic (e.g., airway size in relation to drug particle size), physiologic (e.g., highly variable breathing patterns in infants), pathophysiologic (e.g., presence of inflammation, excess mucus), and behavioral (e.g., inability to synchronize breathing patterns) (Cole, 2000). In addition, characteristics of the aerosol device and the aerosolized drug interact, and both must be taken into account in the development and testing of effective interventions.

In a statement to the committee, the American Thoracic Society cited

the lack of guidance "for the average pediatrician pertaining to the multitudes of delivery devices [tested only in adults] . . . [and] the complexity of treatment of the young infant or toddler. . . . [In general] the smaller the child, the less the dose of aerosolized drug delivered" (ATS, 2004b, p. 2). The group also noted that studies of nebulized drug deposition in very young children who have tracheostomies are rare in the United States due to concerns about approval of the use of radiolabeled drug markers in such studies. They suggested that such studies could be considered under special regulatory provisions that allow the Commissioner of FDA to approve studies of special importance that could not otherwise be approved under research protection regulations that apply specifically to children (see further discussion of these regulations in Chapter 6).

"Working Around" the Lack of a Child-Appropriate Device

For purposes of this discussion, *workarounds* are actions devised to cope with a perceived problem without actually fixing it. Although workarounds may involve doing something new, it is useful to reserve the term *innovation* for a response that is intended not merely to cope with but to solve a problem. Turning off nuisance alarms is a workaround; redesigning an alarm system is an innovation. When workarounds are recognized as insufficient or inefficient responses, they may prompt true innovations.

Common situations that give rise to workarounds include a computer crash or bug (e.g., when a computerized drug order entry system "goes down"), alarms that go off "too" frequently, uncertainty about the appropriate use of equipment (e.g., devices with complex programming procedures), irritating or time-consuming organizational procedures, or unavailability of the right equipment at the right time or at all.

The unavailability of a device properly scaled or otherwise adapted for pediatric use may prompt a workaround. For example, because no stents designed for use in pediatric heart catheterization treatments are commercially available, clinicians use stents in cardiac procedures that were developed for biliary (bile duct) use. This strategy presents some risk of perforation or thrombosis of the targeted vessel (Shaffer et al., 1998). As in this example, workarounds may involve "off-label" or unlabeled uses of medical devices. FDA regulations permit such uses as an element of medical practice and discretion (see Chapter 3).

Another example of a workaround involves the use of a needle designed to aspirate bone marrow to, instead, infuse fluids via infant bone when intravenous access cannot be established during an emergency. The technique has led to different workarounds to stabilize the needle because the needles tend to leak around the entry site unless they are firmly fixed.

Many types of clips or clamps were fashioned to provide secure fixation until recently, when an adjustable "stop" for the needle was devised.

Some workarounds involve the use of devices in ways that are inconsistent with explicit manufacturer instructions because the design of the device makes use consistent with instructions impractical in the real world. For example, alarms for home infusion pumps that signal the presence of air bubbles may be turned off because the alarms respond to small, harmless air bubbles that are common in total parental nutrition fluids. The alarm is then unavailable to detect a larger, potentially fatal air bubble.

Depending on the context, workarounds may be considered either to jeopardize safety (e.g., by disabling alarms or other safeguards) *or* to enhance safety (e.g., by identifying and compensating for a problem until the problem can be investigated and, when possible, fixed) (Mohr and Batalden, 2002). In some cases, the device characteristic or situation that gives rise to a workaround may be reported as an adverse event or close call. In other cases the problem and the workaround may not be thought of as reportable events within either the context of an institutional patient safety program or FDA's program for adverse event reports (see Chapter 7). Workarounds devised by parents or medical caregivers for equipment that is used in the home may never be explained or conveyed back to the manufacturer or even to the prescribing clinicians.

Workarounds may be the norm for extended periods. Sometimes they inspire the development of devices or device adaptations to meet children's needs. For example, the connectors to tracheal tubes add a few milliliters (known as "dead space") to the volume of tubing between the tracheal tube and the connecting tubing of a ventilator. Although this dead space is trivial for a child or adult, it becomes imposing for a tiny premature baby whose breathing volume may only be a few milliliters. To compensate, caregivers often cut the tracheal tube to make it as short as possible, but this makes fixation of the tube tenuous. Now, newer connectors have been designed to reduce the dead space to less than a milliliter.

IDENTIFYING PROBLEMS OR CONCERNS WITH MEDICAL DEVICES USED WITH CHILDREN

Problems with the potential or actual performance of devices in infants, children, and adolescents may be identified in at least three different ways (Box 2.3). First, they may be identified *a priori* based on a combination of expert understanding of children's developmental characteristics and detailed knowledge of the operating characteristics of a particular device derived from theory, bench testing, and, perhaps, animal testing or adult use. For example, engineers identified blood flow problems with downsizing

BOX 2.3
Identifying Concerns or Adaptations with Pediatric Use of a Medical Device (with Examples)

A priori identification

- Pacemaker implant: choice of implant site to minimize potential damage from children's play
- Deep brain stimulator: avoidance of use when patient brain growth is less than 90 percent complete
- Orthopedic fixation device: avoidance of device that will interfere with bone growth

Identification through premarket testing involving children

- Deep brain stimulator: modification of implantation strategy when two neurostimulators are used with small child
- Titanium rib: modification of device and implantation strategy to reduce migration or bone overgrowth

Identification after marketing

- Cochlear implant: association of meningitis with certain devices
- Heart valves from bovine or ovine tissue: accelerated calcification in children leading to early failure
- Cerebrospinal fluid shunt: fractures of peritoneal catheters
- Home apnea monitors: lack of effectiveness in detecting apnea consistently and preventing sudden infant death syndrome

of mechanical heart valves based on theory, past experience with similar devices, simulations, and laboratory tests (Anderson et al., 2000; Bachmann et al., 2000; PSU, 2004). Some makers of cochlear implants have advised against deep-sea scuba diving based on expectations about the possible effects of severe changes in pressure within the ear (Nussbaum, 2003).To cite another example, because children require higher heart rates than adults (approximately 140 beats per minute for infants versus 70 beats per minute for adults), it is anticipated that battery life may be shorter in certain cardiac devices, which makes the prospect of battery exhaustion and planned, serial replacement of devices a reasonable expectation in the pediatric population rather than an unanticipated adverse event (ACC, 2004).

The same process of *a priori* reasoning applies to the identification of important concerns related to the effects of children's growth and development for the number of years that a child has an implant. For example, the developer of the titanium rib built a certain degree of expansion capacity into the device (which requires surgical adjustment) because its purpose is

to facilitate growth in children with severe scoliosis and other conditions that limit chest development. In certain orthopedic repairs, surgeons may remove implanted fixation devices to accommodate children's growth when they might leave such devices undisturbed in mature patients. For yet other implanted devices such as neurostimulators placed in the brain or bone cements used to repair bone defects, concerns about growth and development lead manufacturers and FDA to advise against use of the device with children who have not completed all or most of their growth in areas (e.g., brain, skeleton) where the device is placed.

In addition, pediatric issues or problems may be revealed during clinical testing of a device with children prior to marketing approval. For example, as described earlier in this chapter, studies of deep brain neurostimulators to treat dystonia revealed that use of the device in children, compared to adults, required adaptations in the placement of the device. If two neurostimulators are implanted, they must be implanted at least 8 inches apart to minimize interference.

Problems may be recognized as experience with a device accumulates following its entry into the market. In some cases, problems are identified or confirmed through systematic postmarket clinical or epidemiological studies. For example, in 2002, a manufacturer of cochlear implants reported to FDA 15 cases of meningitis in implanted patients. Subsequently, other manufacturers reported meningitis cases, mostly in young children. Some clinicians had already become concerned about the risk based on conversations at meetings about their experiences following their patients (Niparko, 2004). Based on a review of the adverse event reports, FDA worked with CDC and health departments in many states and three cities on an epidemiologic study that attempted to assess risk factors for meningitis among implant recipients compared to a control group (Reefhuis et al., 2003).

Some problems with devices may be identified soon after they begin to be used with children. To cite an example, the measurement of transcutaneous partial oxygen pressure in arterial blood (measured with an oxygen electrode) was thought to provide a reliable proxy for arterial blood oxygenation (Huch et al., 1977). Soon, however, clinicians recognized that there was a marked disparity between the two values when an infant's perfusion (blood flow into tissues) is poor (Peabody et al., 1978a,b). As this problem was becoming more widely recognized, the pulse oximeter was developed to measure arterial blood oxygenation using a different and superior strategy (Jennis and Peabody, 1987).

Other device problems are uncovered only as clinicians follow patients for extended periods. One example involves problems with fracturing of the peritoneal catheters for cerebrospinal fluid shunts (Langmoen et al., 1992; Cuka and Hellbusch, 1995). The experiences cited above with the

calcification of tissue-based heart valves and the migration of craniofixation devices are additional cases in point.

FDA's regulatory and other activities take each of the modes of problem identification into account. Thus, FDA provides guidance on device design and testing and evaluates information on safety prior to approval or clearance of devices. Through the agency's adverse event reporting program and requirements for postmarket studies of certain devices, it focuses on safety after devices are marketed. As described in this report, these postmarket strategies have serious limitations. Identification and prevention of problems with devices prior to marketing are, in any case, preferable to postmarket detection.

This chapter has provided a pediatric context for a report that often must focus on policies, practices, and questions that are not specific to children. The next reviews the regulatory framework for FDA's activities. With a few exceptions, that framework applies to both adults and children.

3

Regulatory Framework for Postmarket Surveillance of Medical Devices

"As I see it, what the Senator from New York is doing in this particular case is the same thing as if the Congress of the United States should attempt to say by law that calling a sheep's tail a leg would make it a leg . . . if he desires to legislate against these mechanical devices he ought to do it in the open instead of by indirection and attempting to define as a drug something which palpably is not a drug."

Senator Bennett Champ Clark (79 Cong. Rec. 4841, April 2, 1935)

The extension of U.S. Food and Drug Administration (FDA) oversight to devices has been uneven and sometimes has relied on stretching the definition of drugs.[1] Until 1976 when Congress added the Medical Device Amendments (P.L. 94–295) to the Federal Food, Drug, and Cosmetic Act (P.L. 75–717), federal officials had limited explicit authority to regulate the safety or effectiveness of medical devices. In this legislation, Congress provided for additional regulatory scrutiny of medical devices while creating a regulatory framework that recognized certain differences between drugs and devices, particularly the substantial variability in the risk posed by different types of devices.

Virtually the entire regulatory framework for medical devices is general, that is, it applies to devices whether their primary or exclusive use is with adults or children. One exception is that when medical devices are tested with children in studies that will be submitted to FDA, they are usually subject to regulations for the protection of human research subjects that provide special, additional protections for child subjects. Also, in meeting its regulatory responsibilities, FDA may take special notice of children, for example, by limiting the labeled indications for the use of a device to

[1]As described in Chapter 1, the Supreme Court in 1969 sustained FDA's categorization of a laboratory screening device (an antibiotic sensitivity disk) as a drug subject to premarket review (United States v. Bacto-Unidisk, 1969).

adults or directing that pediatric questions be examined in studies following the approval of a device.

This chapter provides a descriptive foundation for the later discussion of the adequacy of FDA's program of postmarket surveillance to protect children. The chapter begins with a brief overview of organizational responsibilities for medical device regulation. It then reviews the premarket regulatory responsibilities of FDA as context for the following description of the agency's responsibilities for postmarket surveillance of medical devices.[2] The last section describes some agency programs and activities, for example, inspections of manufacturers that cover both premarket and postmarket arenas.

ORGANIZATION OF FDA FOR MEDICAL DEVICE REGULATION

Within the Food and Drug Administration, primary responsibility for regulating medical devices (and radiation-emitting electronic products) resides with the Center for Devices and Radiological Health (CDRH). The Center for Biologics Evaluation and Research (CBER) is responsible for regulating medical devices related to blood and cellular products (e.g., kits to test blood for HIV). For combination products that involve a drug and a device or a biological product and a device, the primary regulatory responsibility is assigned to CDRH if the main mode of action of the product is not biological or chemical and does not depend on being metabolized.

Within CDR, the Office of Device Evaluation is responsible for the clearance or approval of medical devices that require premarket review. (The Office of In Vitro Diagnostic Device Evaluation and Safety handles reagents and in vitro diagnostic products.) Another unit, the Office of Science and Engineering Laboratories, contributes to the development of standards and methods for product assessments, performs laboratory evaluations and analyses, and conducts research and testing relevant to medical devices or radiation-emitting electronic products. This unit provides technical support for the development of the device-specific guidance documents as discussed later in this chapter. Although other offices have roles related to postmarket surveillance, the key unit is the Office of Surveillance and Biometrics (OSB). It has three divisions, the Division of Biostatistics, the Division of Postmarket Surveillance, and the Division of Surveillance Systems.

Within OSB, the Division of Postmarket Surveillance oversees the adverse event reporting program, which includes the analysis and investiga-

[2]As noted in Chapter 1, in referring to *premarket* and *postmarket* rather than *premarketing* and *postmarketing* activities, this report follows the legislative language that provided for this study and the usual (but not invariable) practice of FDA in describing activities that occur prior to or following the entry of a medical product into the market.

tion of reports. It also conducts epidemiologic research on the safety and use of medical devices and supports the development of epidemiologic methods for medical device research. As described in Chapter 5, the division has recently assumed responsibility for monitoring postmarket studies required at the time a device is approved for marketing. The Division of Biostatistics provides statistical support for both premarket and postmarket programs and also conducts and collaborates in original research on the health effects of device use. The Division of Surveillance Systems takes the lead in planning, developing, implementing, and maintaining OSB databases and information systems.

Additional support in evaluating device problem reports may be provided by the Division of Device User Programs and Systems Analysis (which is part of CDHR's Office of Communication, Education, and Radiation Programs and which includes FDA's human factors program). The Office of Science and Engineering Laboratories provides technical assistance for premarket as well as postmarket programs.

In addition to its central offices in Maryland, FDA has more than 160 field offices, laboratories, and other sites throughout the country. These sites house most of the agency's Office of Regulatory Affairs employees who are responsible for various enforcement activities (e.g., seizures of adulterated foods or medical products) and for inspections of medical product, food, and cosmetic manufacturers (FDA, 2003g). Table 3.1 shows CDRH budget authority and total funding levels for FY 1994 to FY 2004.

TABLE 3.1 Budget Authority and Total Program Level Funding History for Center for Devices and Radiological Health FY 1994–2005 (in millions)

Year	Budget Authority (Center and Field)	Total Program Level (Budget Authority plus User Fees)
1994	$159	$159
1995	157	170
1996	144	152
1997	147	160
1998	144	156
1999	147	159
2000	158	170
2001	173	186
2002	180	194
2003	193	217
2004	191	222

NOTE: Program level funding includes user fees from inspections of mammography facilities and, beginning FY 2003, fees provided for under the Medical Device User Fee and Modernization Act of 2002.
SOURCE: FDA Congressional Justification submissions (data compiled by CDRH staff).

The fiscal year 2004 budget for OSB postmarket surveillance activities was approximately $15 million, approximately half of which covered costs for about 70 full-time equivalent staff positions, including approximately 50 positions devoted to postmarket surveillance specifically (personal communication, Thomas P. Gross, M.D., Director, Division of Postmarket Surveillance, CDRH, October 1, 2004, and April 6, 2005). About one-third of the budget involved the MedSun program, which is described later in this chapter. The budget includes no funds for the analysis of outside data sources, such as Medicare databases or professional society registries.

BASICS OF PREMARKET REGULATION OF MEDICAL DEVICES

The premarket regulatory processes of FDA include evaluations, decisions, and other actions that occur prior to the marketing of a medical product. In some cases, requirements are established before or at the time of marketing approval for actions that will take place after marketing, for example, when further clinical studies are specified as a condition of FDA's approval of a device.

When Clearance or Approval of a Device Is Required

According to FDA, approximately 20,000 American and foreign firms produce about 80,000 brands and models of medical devices for the U.S. market (FDA, 2002b). Before they can be marketed in the United States, roughly 55 to 60 percent of medical devices require FDA clearance or approval.

The requirements that must be met for a device to be legally marketed in the United States depend in considerable measure on its risk classification. The Medical Device Amendments of 1976 provided that devices be classified—in ascending order of risk—as Class I, II, or III devices (21 USC 360c). FDA completed the basic process of classifying existing devices into the three groups by 1988 (Merrill, 1994). In 2004, the three classes accounted for about 43 percent, 44 percent, and 13 percent of classified devices, respectively (personal communication, Donna-Bea Tillman, Ph.D., Deputy Director, Office of Device Evaluation, CDRH, January 18, 2005; see also FDA, 2004n).[3] Table 3.2 provides examples of common pediatric-use devices in the three classes.

[3]The 13 percent figure includes Class III devices that require premarket approval.

TABLE 3.2 Examples of FDA Class I, II, and III Devices

Device Class	Examples
I	Bassinets
	Nursing bottle nipples
	Infant caps
	Mechanical toothbrushes
	Circumcision trays
	Mechanical wheelchairs
II	Neonatal incubators
	Dialysis catheters
	Circumcision clamps
	Powered wheelchairs
	Apnea monitors
	Transcutaneous electrical nerve stimulators
	Ventriculoperitoneal shunts
III	Implantable insulin pumps
	Implantable cardiac pacemakers
	Ventricular assist devices
	Cochlear implants
	Deep brain stimulators

Class I Devices

Class I devices are considered to present relatively low risk to patients. As specified in statute (21 USC 360c(a)(1)(A)), this class covers

- devices for which certain "general" controls (e.g., standards for good manufacturing practices) provide reasonable assurance of the safety and effectiveness of the device or
- devices that are not intended or represented ("purported") to support or sustain life or play an important role in preventing impairment or that are not expected to pose an unreasonable risk of illness or injury.

General controls apply to Class II and Class III as well as Class I devices. These controls are discussed further below.

Nearly all Class I devices and some Class II devices may be marketed without FDA clearance or approval. Examples of Class I devices that *are not* exempt from review under the notification procedures outlined below are dental mercury, mechanical wheelchairs, and surgeon's gloves (FDA, 2005e,f,g). If a device that is normally exempt from FDA premarket clearance is to be marketed for a new intended use or involves a new fundamental technology, it would require a premarket clearance.

Class II Devices

Devices categorized as Class II present more risk than Class 1 devices. For a Class II device to be legally marketed, the manufacturer must usually submit a notification of intent to market and receive FDA clearance under "510(k)" provisions (referring to the applicable section of the Federal Food, Drug, and Cosmetic Act, 21 USC 360(k); see also FDA, 2004w). These 510(k) provisions cover devices that are "substantially equivalent" to a "predicate" or "pre-amendment" device, which is one that was either marketed before May 28, 1976 or one that has been shown (through the notification and clearance process) to be substantially equivalent to such a device.[4]

FDA considers a device substantially equivalent if it has the same intended use and the same technological characteristics as the predicate (pre-amendment) device. A device may also be considered substantially equivalent when it has the same intended use but different technological characteristics *if* these differences do not raise different questions of safety and effectiveness *and if* information (which can include clinical data) is provided to show that the device is as safe and effective as a legally marketed device. This latter definition allows FDA "the flexibility to clear some fairly novel devices through the 510(k) process" (Kahan, 1996, p. 89).

In assigning devices to Class II, FDA has determined that (1) general controls are not by themselves sufficient to provide reasonable assurance of safety and effectiveness, but (2) sufficient information is available to develop special controls for that purpose. These controls are discussed below.

For certain Class II devices, FDA issues guidance documents that describe what kinds of bench, animal, and clinical data should be submitted to show that a device is substantially equivalent to a predicate (preamendment) device. In 2002, for example, the agency issued guidance for manufacturers of carbon dioxide and oxygen monitoring devices about the kinds of information they should submit to document safety and effectiveness as part of a 510(k) submission (FDA, 2002d). Submission of clinical data is required for about 10 to 15 percent of devices covered by the 510(k) process (Tillman and Gardner, 2004). FDA also has the authority to require further studies for devices that are covered by regulations authorizing postmarket surveillance studies as discussed below.

[4]The provisions also apply to pre-amendment devices that have been classified as Class III devices but for which FDA has not yet issued regulations calling for premarket approval applications. A few Class II devices are exempt from the provisions, including pediatric hospital beds, enuresis alarms, and hematocrit measuring devices (FDA, 1998j).

Class III Devices

Class III devices are intended to support or sustain life or play an important role in preventing impairment or are considered to pose an unreasonable risk of illness or injury. For devices in this class, FDA has determined that general controls are inadequate to reasonably assure safety and effectiveness and that available information is insufficient to develop adequate special controls.[5] As indicated by percentages cited earlier, many more devices enter the market through the clearance process than through the approval process (more than three times as many in 2004).

Usually, manufacturers of Class III devices must submit premarket approval (PMA) applications to FDA. As part of such applications, they must present the results of investigations—including data from clinical studies—that support the device's safety and effectiveness for the use or uses proposed. After a device is approved, changes in the device, its labeling or packaging, or its manufacturing may require approval under a supplemental PMA application if the changes affect safety or effectiveness. Such supplemental applications also cover changes or other actions related to any postmarket studies that were required as a condition of approval of a device.

The 1997 legislation provided that manufacturers have an opportunity to meet with FDA to discuss their clinical investigation plan prior to submitting a PMA application. They may request a "determination meeting" to discuss what kind of scientific evidence (e.g., a randomized clinical trial) FDA considers necessary to demonstrate that a device is effective for its intended use. The resulting determination is binding on the agency, unless it is subsequently judged to be "contrary to public health" (FDA, 2001d, p. 1). In addition, the legislation provided the opportunity for an "agreement" meeting to those planning a PMA application or a 510(k) submission for certain devices. The purpose of such a meeting is to reach agreement on the main elements of the investigational plan, including the clinical protocol. The results of an agreement are again binding in most circumstances.

An alternative to the PMA application is the product development protocol (PDP), which was provided for by the 1976 Medical Device Amendments but not implemented until the 1990s (FDA, 1999e). The PDP pathway allows a manufacturer, with FDA agreement, to consult with FDA

[5]A new device may also be automatically classified as a Class III device because no predicate device exists, that is, the new device is not substantially equivalent to any other Class I or Class II device marketed before May 28, 1976, or to any device that was placed into Class I or Class II after that date. If a device is automatically classified into Class III because no predicate device exists to which it can be claimed equivalent *and* if the device presents a low risk to patients, the FDA Modernization Act of 1997 allows FDA to reclassify the device into Class I or II under a "de novo" or "risk-based" procedure (FDA, 1998k).

to develop and implement a mutually acceptable device development testing protocol for a device. The manufacturer can then secure approval by submitting and having FDA accept a notice that it has fulfilled the requirements of the protocol.[6] FDA considers this pathway appropriate for "those devices in which the technology is well established in industry" (FDA, 2003c, unpaged).

To comply with the FDA Modernization Act of 1997 (P.L. 105–115), FDA revised procedures for expedited review of PMA applications. Expedited review is allowed for devices that are intended to treat or diagnose life-threatening or irreversibly debilitating diseases or conditions and that also represent (1) breakthrough technologies, (2) technologies for which no approved alternatives exist, (3) technologies that offer significant advantages over existing approved alternatives, or (4) technologies the availability of which is in the best interest of patients (FDA, 2003i). Expedited review may involve advance consultation with FDA. (Provisions for expedited review also exist for products requiring premarket clearance.)

When a device is approved for marketing, FDA may impose requirements for further study of or reporting about a device to expand knowledge about its safety or effectiveness (21 CFR 814.82). These required studies are often referred to as condition-of-approval or post-approval studies. These studies and their monitoring by FDA are discussed further in Chapter 5.

Investigational Devices

For certain devices that have not been approved or cleared for marketing or that are being tested for indications not previously approved or cleared, use of the device during testing occurs under an "investigational device exemption" or IDE (21 USC 360j(g); 21 CFR 812.2(c)). An IDE is required for a "significant risk" device, which regulations define as one that presents a potential for serious risk to the health, safety, or welfare of a research participant (21 CFR 812.3(m)).[7] The IDE regulations specifically

[6]The protocol is to include a description of (1) the device, including modifications; (2) any preclinical or clinical studies completed, underway, or planned; (3) manufacturing methods, facilities, and controls; (4) applicable performance standards, if any; (5) proposed labeling; and (6) other information deemed necessary by FDA. The manufacturer must also submit progress reports and information on studies described in the protocol.

[7]FDA may allow clinical use of unapproved devices in other situations, including certain emergency situations and certain situations in which a clinical study has been completed but the marketing application has not yet been approved. In addition, under so-called "compassionate use" provisions, FDA may allow use of an investigational device when it might benefit a patient who does not meet criteria for inclusion in research but who has a serious medical condition and no satisfactory alternative (FDA, 2003e).

mention the potential for serious risk related to implants, life-supporting or life-sustaining devices, and devices that are substantially important in preventing impairments in health.

An IDE application must include information on preclinical studies and any already available clinical data. The sponsor must also submit an investigational plan that describes the research design and analytic methods to be used. The study cannot proceed until the IDE is approved by FDA and an Institutional Review Board (IRB).[8] For studies involving significant risk devices, FDA and investigators or sponsors may engage in extensive communication and negotiation about the characteristics and objectives of research studies to support claims of product safety and effectiveness.

An IDE application is not required for a "non-significant risk" device study. The sponsor must, however, comply with certain recordkeeping and reporting requirements. In addition, even if an IDE is not required, research involving human participants is still subject to certain other requirements, including IRB review (see, e.g., FDA, 2003d). A study involving a "non-significant" risk device is said to have an "abbreviated IDE" or "deemed approved IDE."

Humanitarian Use Devices

In addition to the clearance and approval processes described above, Congress has allowed devices to be approved for marketing under a Humanitarian Device Exemption (HDE). To qualify, a device must be intended for patients with a rare disease or condition for which no comparable device is available that has a 510(k) clearance or an approved PMA application for the proposed indication (21 USC 360j(m)). "Rare" is defined to mean that the condition affects or is manifested in (causes symptoms in) fewer than 4,000 individuals in the United States per year. Among other requirements, manufacturers seeking an HDE must present evidence that (1) provides a reasonable assurance of product safety when the device is used as proposed and (2) indicates that the probable health benefits of the device outweigh the potential for harm, taking into account the risks and probable benefits of available alternative therapies. Evidence of effectiveness is not required.

Granting of an HDE allows a company to market a device as a Humanitarian Use Device (HUD). Except in certain emergency situations, such a

[8]An IRB is a group of qualified individuals charged under federal regulation with protecting the rights and welfare of people involved in research in accord with federal regulations. IRBs review and approve plans for research involving humans.

device can only be used in a health care facility following IRB approval and continuing review. (The IRB may approve use of the device on a case-by-case basis or under a research protocol or without any further restrictions.)

As is the case for a PMA application, FDA may order a manufacturer to conduct further studies as a condition of approval for an HDE (21 CFR 814.126(a), 814.82(a)(2)). For example, when FDA approved an HDE for the use of a left ventricular assist device with children, it required that the first 50 children receiving the device be followed to heart transplantation, death, or other outcome.

Least Burdensome Approach

The FDA Modernization Act of 1997 specified that the procedures and information required of manufacturers to demonstrate substantial equivalence for 510(k) clearance involve the "least burdensome means" for such demonstration (21 USC 360c(i)(1)(D)). Likewise, for devices requiring premarket approval, regulators are to "consider, in consultation with the applicant, the least burdensome appropriate means of evaluating device effectiveness that would have a reasonable likelihood of resulting in approval" (21 USC 360c(a)(3)(D)(ii)). Although the statutory provisions involve premarket clearance and approval processes, FDA has said it will apply the least burdensome concept to postmarket and other activities as well (FDA, 2002q, unpaged).

In attempting to put the least burdensome concept into practice, FDA has stated that it would apply these basic principles. First, "[t]he basis for all regulatory decisions will be found in sound science and the spirit and the letter of the law." Second, "[i]nformation unrelated to the regulatory decision should not be part of the decision-making process." Third, "[a]lternative approaches to regulatory issues should be considered to optimize the time, effort, and resources involved in resolving the issue consistent with the law and regulations." Fourth, "[a]ll reasonable measures should be used to reduce review times and render regulatory decisions within statutory timeframes." (All text quoted from FDA, 2002q.)

User Fees

In the Medical Device User Fee and Modernization Act of 2002 (P.L. 107–250), Congress authorized FDA to charge a fee for the review of 510(k) submissions and PMA applications. One major objective was to help speed the clearance or approval of devices by augmenting FDA resources. In contrast to the provisions for prescription drug user fees, device user fees are expressly allowed to be used for evaluating condition-of-approval postmarket studies and identifying safety and effectiveness issues

for devices (see 21 USC 379i(5)(j) and (k) and 21 USC 379j(h)(2)(A)(ii) for devices compared to 21 USC 379g(6) for drugs).

The legislation provided a complete waiver of fees for certain reviews involving pediatric use of a device. Specifically, if a company seeks clearance or approval of a device solely for pediatric use, the fee may be waived. If the company later seeks to add an adult indication, the user fee would be assessed at the regular level for a PMA review. If, however, a company has a device that has been cleared or approved for an adult indication and then seeks clearance or approval for a use that involves only a pediatric population, the fee may be waived.

According to FDA, 32 applications for FDA approval or clearance were exempted from user fees in FY 2004 (personal communication, Heather Rosecrans, Director, Premarket Notification, Office of Device Evaluation, CDRH, January 18, 2005). Two applications involved premarket approvals; the other 30 were applications for clearance under 510(k) procedures (7 of which involved a determination that the product in question was not a device). User fees do not apply to requests for Humanitarian Device Exemptions.

Off-Label or Unlabeled Use of Devices

A typical FDA letter granting approval of a PMA application states the indications for use of the device. Sometimes the approval letter may note limitations, for example, that the use is for those over a certain age. Likewise, each 510(k) clearance letter includes an accompanying "indications for use" page that states the cleared indications and any limitations on use (FDA, 2002f).

Once a device is approved or cleared, physicians may use the device for indications that are not mentioned in the device's labeling but are not specifically restricted. Such use is sometimes called "off-label" or "unlabeled" use (see, e.g., FDA, 1998c, 2002f). It is considered part of the practice of medicine, which FDA—by statute—does not regulate (21 USC 396; FDA, 1998h).

When General or Special Controls Apply

General controls apply to all three classes of medical devices (FDA, 1998d). They include requirements for actions both prior to and after a device reaches the market. General controls require device manufacturers to

- register each manufacturing location with FDA;
- list their marketed devices with FDA;
- comply with device labeling regulations;

- submit premarket notifications unless exempt;
- follow quality system regulations (which incorporate good manufacturing practice requirements) in device production;
- adhere to regulations banning adulterated and mislabeled devices;
- comply with regulations related to record keeping and reporting; and
- follow FDA requirements related to any notifications, recalls, or other actions associated with a defective device.

FDA can exempt Class I devices from certain general controls, including most quality system regulations/good manufacturing practices (21 USC 360c(d)(2)(A)). Examples of Class I devices that are exempt from most such practices are components of casts (e.g., a cast heel or cast toe cap), manual toothbrushes, mechanical walkers, and tuning forks used to test for hearing disorders (FDA, 2004r). Quality system regulations, which apply both prior to and following the marketing of most devices, are discussed further at the end of this chapter.

Special controls are intended to ensure the safety and effectiveness of Class II devices when general controls are not adequate to do so. Specific controls vary by device type. They may include special labeling requirements, guidance documents, performance standards, and required postmarket studies.

Labeling requirements vary for different kinds of devices. Generally, a device label must contain information about the name and place of business of the manufacturer and the device's intended use or uses. The labeling should also include adequate directions for the safe use of the device. Devices aimed at patients or lay caregivers are to have labels that these individuals can understand and use whether or not they have also received instructions from health care professionals (FDA, 2001g). For some categories of devices, such as hearing aids, latex condoms, and menstrual tampons, FDA has established specific user or professional labeling requirements as well. In addition to the usual information about intended uses, hazards, contraindications, and similar matters, labels for investigational devices must state that they are limited by law to such uses (21 CFR 812.5(a)).

Mandatory performance standards have been developed for only a handful of product categories involving electronic or radiation-emitting products, some of which (e.g., microwave ovens and cell phones) are not medical devices (21 CFR 1010–1050).[9] The only standard for a medical

[9]In 1995, FDA issued a proposed rule to establish a mandatory performance standard for apnea monitors, but the agency withdrew the rule in 2000 (FDA, 2000d). At the same time, it issued a guidance document on the monitors that described minimum performance, testing, labeling, and clinical criteria (FDA, 2000a).

device is that for electrode lead wires and patient cables (FDA, 1997a). Rather than promulgating mandatory performance standards, FDA has focused on cooperation with other countries and private groups to develop national and international voluntary, consensus standards (Phillips and Less, 1999; see also Merrill, 1994).

Based on provisions of the Safe Medical Devices Act of 1990 (P.L. 101–629), FDA has developed special control guidance documents for several kinds of Class II devices. For example, when it created a separate device category for apnea monitors (to distinguish these devices from the generic category of breathing frequency monitors), FDA presented minimum performance, testing, and labeling recommendations (FDA, 2002m). Other special control guidance documents have been issued in conjunction with the reclassification of a device from Class III to Class II, as was recently done for arrhythmia detector and alarm devices (FDA, 2003h).

Another type of special control, Postmarket Surveillance (as narrowly defined in section 522 of the Federal Food, Drug, and Cosmetic Act) may be ordered by FDA for certain Class II or Class III devices. These orders, which can include the collection of clinical data, are discussed further below and in Chapters 5 and 6. In a 1998 document discussing the elimination of statutory requirements for Section 522 Postmarket Surveillance for certain devices, FDA stated that it "will consider the potential to collect postmarket surveillance data to allow more rapid progress [of a device] to market" (FDA, 1998g, p. 1).

In addition, as a condition of approval for a device that requires premarket approval, manufacturers are to provide FDA with an annual report that describes any changes made to the device during the reporting period. The report must also include a bibliography and summary of published and unpublished reports (that were not part of the PMA application) of clinical or laboratory studies involving the device or similar devices (21 CFR 814.84(b)(2)). (These requirements do not apply to devices cleared under 510(k) provisions.) In certain cases, FDA may request copies of the reports. The summary does not in itself amount to an assessment of the information reported.

BASICS OF POSTMARKET SURVEILLANCE

In this report, postmarket surveillance for medical devices refers primarily to activities that may be required or promoted by FDA or voluntarily undertaken by manufacturers or others to learn more about the safety and effectiveness of marketed medical devices and to respond to safety concerns. Some surveillance activities such as adverse event reporting cover all classes of medical devices whereas others, notably required postmarket surveillance studies, are restricted to a small subset of devices.

As described in more detail below, FDA's postmarket surveillance programs include adverse event reporting and analysis, medical device tracking for certain devices, and focused studies of selected products, including epidemiologic and other analyses undertaken or supported by FDA and studies required of manufacturers. When surveillance activities identify an important problem with a device, FDA is also responsible for identifying an appropriate response, for example, a public notice suggesting precautions for physicians or a request that a manufacturer recall a product.

Beyond these kinds of regulatory postmarket programs, many kinds of knowledge-building activities may occur after a device is approved for marketing. Such activities may be undertaken or funded by manufacturers or by other government agencies (e.g., National Institutes of Health [NIH] or Veterans Administration) for primary purposes other than surveillance. Such purposes include expanding the evidence base for clinical decisions, supporting coverage decisions by Medicare or other payers, identifying less costly ways of delivering health care, or extending the indications for use for which a device is explicitly approved. Thus, a manufacturer's self-initiated postmarket study of a device to support FDA approval of a new use arguably does not meet the definition of surveillance, although such a study might generate information, including adverse event reports, that is also relevant to approved indications. Likewise, the investigation of radiation doses to children from repeated computer-assisted tomography might be undertaken in the first instance to generate knowledge to guide clinical practice, but such knowledge might also prompt adaptations by manufacturers of these devices and safety guidance from FDA (see, e.g., Feigal, 2001b).

In addition to clinical studies, clinicians may present or publish case reports of patients who have had a device-related problem that fits the definition of an adverse event. Although these clinicians may not knowingly be engaged in surveillance, their case reports may prompt attention from FDA or manufacturer surveillance programs. One challenge for FDA and for others interested in early warning of potential safety problems involves how to take better advantage of physician experiences in recognizing such problems without creating unduly burdensome or unproductive procedures or programs. Chapter 4 returns to this issue.

Mandatory and Voluntary Adverse Event Reporting

The Federal Food, Drug, and Cosmetic Act authorizes FDA to establish a system for the reporting of adverse events associated with legally marketed medical devices (21 USC 360i). Current FDA programs, which cover all classes of medical devices, provide for mandatory reporting from manufacturers, importers, and user facilities and voluntary reporting from others, including consumers and health care professionals. (Chapter 4 looks at adverse event reporting in more depth.)

The objective of adverse event reporting is to gain information about a medical device that assists FDA in protecting the public's health by helping "to assure that such device is not adulterated or misbranded and to otherwise assure its safety and effectiveness" (21 USC 360i(a)). Although the statute uses the words "safety and effectiveness," the specific reporting requirements focus on safety.

Mandatory Medical Device Reporting Program

In response to the Medical Device Amendments of 1976, FDA created the Mandatory Medical Device Reporting (MDR) program (21 CFR 803) for device manufacturers and importers.[10] The implementing regulations became effective in 1984.[11] The Safe Medical Devices Act of 1990 expanded reporting obligations to cover hospitals and other "user facilities" and device distributors. The Medical Device Amendments of 1992 (P.L. 102–300) added definitions of certain terms and established a single reporting standard for device manufacturers, distributors, and user facilities. Subsequently, the FDA Modernization Act of 1997 eliminated most reporting requirements for distributors, although they are required to maintain complaint files that include reports of adverse events (FDA, 2001i; 21 CFR 803.18(d)). The 1997 amendments also provided for a new surveillance system for user facilities as described later in this chapter.[12]

[10]In 1973, FDA created a limited, voluntary adverse event reporting program, the Medical Device Laboratory Product Problem Reporting Program (PRP). The program was replaced by the mandatory program in 1984 (Gardner and Flack, 1999).

[11]In addition to these requirements, FDA also requires reporting of adverse device reaction and device defect reports under regulations specifying post-approval requirements for manufacturers that are intended "to provide reasonable assurance, or continued reasonable assurance, of the safety and effectiveness" of an approved device (21 CFR 814.82(a)(9)). Reporting is required when the manufacturer learns of (1) a "mix-up" of the device or its labeling with another product; (2) an "adverse reaction, side effect, injury, toxicity, or sensitivity reaction that is attributable to the device" and that either is not covered by the device's labeling or is covered by labeling but is unexpectedly more severe or frequent; or (3) "any significant chemical, physical or other change or deterioration in the device, or any failure of the device to meet the specifications established in the approved PMA that could not cause or contribute to death or serious injury but are not correctable by adjustments or other maintenance procedures described in the approved labeling" (FDA, 2002e, unpaged). If the deterioration or other change can be corrected by procedures described in the device's labeling, then the manufacturer can report the event in its annual report. If reporting is required under these provisions and the MDR provisions, FDA specifies that the MDR provisions shall apply so that duplicate reports are not submitted.

[12]As of July 13, 2005, a "plain language" statement of the reporting rules was in effect, which might change some citations of regulations in this chapter (Federal Register, June 15, 2005, p. 34652).

BOX 3.1
Selected Definitions Related to Medical Device Reporting Requirements

Manufacturer
One who manufactures, prepares, propagates, compounds, assembles, or processes a device by chemical, physical, biological, or other procedure. Also includes U.S. agents of foreign manufactures, those who establish specifications for devices manufactured by another party and who then distribute those devices, and those who repackage or otherwise change the container, wrapper, or labeling of a device.

Importer
One who imports a device into the United States and who furthers the marketing of a device from the original place of manufacture to the person who makes final delivery or sale to the ultimate user. Does not include those who repackage or otherwise change the container, wrapper, or labeling of the device or device package.

Distributor
One who furthers the marketing of a device from the manufacturer to the entity that makes final delivery or sale to the ultimate user.

Device user facility
A hospital, ambulatory surgical facility, nursing home, outpatient diagnostic facility, or outpatient treatment facility.[a] Does not include physician's offices, school nurse offices, or employee health units.

Reportable event
(1) An event about which a user facility becomes aware of information that reasonably suggests that a device has or may have caused or contributed to a death or serious injury; or
(2) An event about which a manufacturer or importer has received or become aware of information that reasonably suggests that one of its marketed devices:
(a) may have caused or contributed to a death or serious injury; or
(b) has malfunctioned and that the device or a similar device marketed by the manufacturer or importer would be likely to cause or contribute to a death or serious injury if the malfunction were to recur.

Box 3.1 defines several terms used in the reporting regulations. Under FDA regulations, home health care agencies are considered to be user facilities. Those who supply medical equipment to patient's homes are considered to be distributors.

Box 3.2 summarizes adverse event reporting requirements for medical

Serious injury
: An injury or illness that (1) is life threatening, (2) results in permanent impairment of a body function or permanent damage to body structure, or (3) requires medical or surgical intervention to preclude permanent impairment or damage.

Caused or contributed
: When a death or serious injury was or might have been attributed to a medical device or when a medical device was or might have been a factor in a death or serious injury, including events that result from
  (1) failure,
  (2) malfunction,
  (3) improper or inadequate design,
  (4) manufacture,
  (5) labeling, or
  (6) user error.

User error[b]
: An error made by the person using the device that may be the sole cause of or merely a contributor to a reportable event.

Complaint
: A written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a device after it is released for distribution.

Remedial action
: An action, other than routine maintenance or servicing of a device, that is necessary to prevent recurrence of a reportable event.

---

[a]Nursing homes primarily provide skilled nursing care and related services for persons who require medical or nursing care. They may also provide hospice care to the terminally ill or rehabilitative services. Outpatient treatment facilities provide nonsurgical therapeutic (medical, occupational, or physical) care on an outpatient basis or in a home health care setting. The category includes ambulance providers, rescue services, and home health care agencies.

[b]The term "user error" was defined in a guidance document rather than regulations (FDA, 1997b). The generally preferred term is now "use error," which is consistent with a systems perspective that deemphasizes individual blame for errors and focuses on circumstances that put users of a device at risk of making errors.

SOURCES: 21 CFR 803.3 and 820.3(b).

device manufacturers and importers.[13] In general, regulations require that they (1) report deaths and serious injuries that a device has or may have

[13]For a device designed and labeled for single use that is reprocessed, the manufacturer for purposes of adverse event reporting is the entity that does the reprocessing (e.g., a reprocessing company or a health care facility that does its own reprocessing) (FDA, 2004q).

BOX 3.2
Medical Device Reporting Requirements for Device Manufacturers

1. Report individual adverse events to FDA within 30 calendar days after learning of a reportable death, serious injury, or device malfunction;
2. Report individual adverse events within 5 working days after learning of (a) an event that requires remedial action to prevent an unreasonable risk of substantial harm to the public health or (b) an event for which FDA has made a written request for reports;
3. Submit supplemental reports within 1 month after obtaining additional information that was not provided in an initial event report;
4. Submit baseline reports that provide basic information (e.g., brand name, model number) about a device after the first reportable event involving that device;
5. Provide annual updates of changes in baseline information;
6. Maintain complete medical device reporting files that include, among other items, information about deliberations and processes used to determine whether an event was reportable; and
7. Develop and follow written procedures for reporting adverse events.

SOURCES: 21 USC 360i; 21 CFR 803.10; FDA, 1997b, 2000f.

caused or played a role in causing, (2) report device-related malfunctions that could cause a death or serious injury, (3) establish and maintain adverse event and complaint files, and (4) submit certain follow-up or summary reports to FDA. In contrast to the provisions for adverse drug event reporting, the reporting requirements for medical devices do not distinguish between expected (e.g., listed in a drug's labeling) and unexpected adverse events (21 CFR 314.80; FDA, 2001f).

In their reports, manufacturers must include information about whether a device was returned and evaluated, the method and findings of evaluation, and any remedial action such as a recall or labeling change. In addition to requirements for adverse event reporting, separate "quality system" regulations include requirements for timely review and evaluation of complaints and for maintenance of complaint files (21 CFR 820.198).

Manufacturers are not required to report all complaints or information received but rather must evaluate this information to determine whether it involves a reportable event. Companies may receive information or complaints by telephone, fax, mail, or e-mail from consumers, health care workers, health care facilities, vendors, or their own sales or service representatives or other employees. They may also become aware of possible problems through scientific articles, news reports, professional conference presentations, or communications from FDA or other government agencies.

BOX 3.3
Medical Device Reporting Requirements for User Facilities

1. Report to both FDA and the manufacturer within 10 working days any death that a device might have caused or to which it might have contributed;
2. Report to the manufacturer (or to FDA if the manufacturer is not known) within 10 work days any serious injury that a device might have caused or to which it might have contributed; and
3. Provide annual summary to FDA of the number of adverse events (deaths or serious injuries) reported to FDA or manufacturers.

SOURCES: 21 USC 360i; 21 CFR 803; FDA, 2001i.

Box 3.3 summarizes reporting requirements for user facilities (as defined in Box 3.1). (The requirements apply to devices, but not to drugs or biologics for which reporting is voluntary.) User facilities must report deaths to both FDA and the manufacturer but need to report serious injuries to FDA only if they do not know the manufacturer of the device. Unlike manufacturers, facilities are not required to report device malfunctions unless they actually cause death or serious injury. That is, they need not report close calls that had the potential to cause serious harm, although reporting of such close calls is increasingly recognized as providing an opportunity to make changes in systems or devices to prevent harm (see, e.g., IOM, 2000c; Wald and Shojania, 2001a). In addition, the regulations do not require facilities to investigate adverse events, although they may do so under their own patient safety policies and procedures or voluntary accreditation standards.

FDA has emphasized that the privacy provisions of the Health Insurance Portability and Accountability Act of 1996 (P.L. 104–191) should not "disrupt or discourage adverse event reporting" (FDA, 2003b, unpaged). That legislation explicitly allows for the reporting to FDA and manufacturers of adverse events and other information related to the quality, effectiveness, and safety of FDA-regulated products. The forms and procedures for mandatory reporting are described further in Chapter 4.

The adverse event reporting regulations described above do not apply to investigational devices. Rather, FDA regulations that govern use of investigational devices require that researchers report any adverse device "effect" to the research sponsor and the Institutional Review Board that approved the research (21 CFR 812.150; see also 21 CFR 812.46(b)). Sponsors are then to evaluate such reports and, in turn, report "unanticipated adverse device effects" to FDA and all participating investigators and review-

ing IRBs. Some clinical trials have special data monitoring committees (or—in NIH terminology—data and safety monitoring boards) with special responsibilities for monitoring the safety of clinical trials, including evaluating adverse event reports and outcome data. FDA has issued guidance on the use of such bodies (FDA, 2001c).

Alternative Summary Reporting for Manufacturers

Although required reporting is not limited to unexpected adverse events involving medical devices, FDA is most interested in the detection of unexpected, serious problems or recognized problems that are occurring more frequently than expected (e.g., given the data from clinical studies on which marketing approval was based). FDA has created an Alternative Summary Reporting program that allows manufacturers to submit abbreviated reports for certain well-known and well-documented problems. Examples include breast implant ruptures and shearing of central line catheters (FDA, 2004b).

Approximately 80 manufacturers and 40 different types of classified devices were participating in this alternative reporting program in 2004 (personal communication, Thomas P. Gross, M.D., Director, Division of Postmarket Surveillance, CDRH, October 8, 2004). Participation in the program requires FDA agreement (FDA, 2000c). Summary reports do not include information that allows identification of events involving children.

Voluntary Reporting for Health Professionals and Consumers

In addition to the mandatory reporting requirements for manufacturers, importers, and user facilities, FDA also provides health professionals and consumers the opportunity to report adverse events on a voluntary basis through its MedWatch program.[14] (See Chapter 4 for further discussion.) MedWatch covers drugs, biologics, and nutritional supplements as well as devices. It also provides information about medical product safety, including recall announcements and safety advisories. The introductory online reporting information provided to health care professionals emphasizes that MedWatch is not to be for reporting adverse events associated with clinical studies, vaccines, veterinary products, or mandatory reporting

[14]The MedWatch website also includes information and forms for mandatory reporting. FDA uses the term medical device reporting or MDR to refer to mandatory reporting while describing MedWatch as its program for voluntary reporting for consumers and health professionals (FDA, 2002l). The MedWatch website, however, has the banner "The FDA Safety and Adverse Event Reporting Program" (see website at http://www.fda.gov/medwatch/).

situations (FDA, 2004z). A separate reporting system exists for vaccines, the Vaccine Adverse Event Reporting System (VAERS), which is managed jointly by FDA and the Centers for Disease Control and Prevention (CDC).[15]

Adverse Event Information Available to the Public

FDA maintains electronic files of adverse event reports for its own use. It makes a subset of the information available for public access. The Manufacturer and User Facility Device Experience (MAUDE) database includes all voluntary consumer and professional adverse event reports since June 1993, user facility reports since 1991, distributor reports since 1993, and manufacturer reports since August 1996. Manufacturer reports for 1992 through July 1996 are maintained in the Device Experience Network database.

Before information from adverse event reports is made available to the public, FDA deletes

- information involving trade secrets or confidential commercial or financial data;
- personal medical or other information (including the serial number of implanted devices) that could identify individual patients or family members; and
- identifying information about consumers or health care workers who submit a voluntary report.

To protect patient privacy, records in the FDA public file do not include categories of potentially identifying patient information from the reporting forms, for example, patient birth date, age, weight, or sex. In some cases, the narrative information for an individual adverse event report may make it evident (by using terms such as child, baby, or infant) that a child was involved. Although FDA staff have access to the complete information, the deletions mean that users of the public files are more limited in their ability to identify reports involving children. As noted above, HIPAA

[15]Congress established VAERS in the National Childhood Vaccine Injury Act of 1986 (P.L. 99–660). The legislation required health professionals as well as manufacturers to report, and reports are also submitted by state and local health departments and by patients and parents. Following direct mailings, continuing medical education, and other efforts to increase reporting by professionals, the proportion of all reports that were attributed to health care professionals increased from 11 percent in 1991 to 35 percent in 2001 (Zhou et al., 2003). The 1986 legislation also created a no-fault compensation system for people thought to have been injured as a result of certain recommended childhood immunizations.

privacy provisions explicitly allow for adverse event reporting as set forth in FDA regulations. (Confidentiality and trade secret issues are discussed further below.)

Pilot Program for Adverse Event Reporting: MedSun

As discussed in Chapter 4, passive surveillance systems have a number of limitations as means of monitoring the safety of medical devices after they have reached the market. Limitations in user facility reporting have been a particular concern. According to FDA, manufacturers reported 980 device-related deaths to the agency in 1998 while user facilities reported 277 such deaths that year. FDA concluded that the discrepancy between the two figures is "one measure of underreporting" by user facilities (Gardner and Flack, 1999, unpaged).

The FDA Modernization Act of 1997 directed FDA to develop a new system for adverse event reporting by a subset of user facilities that offers a "representative profile of user reports" of deaths and serious illnesses or injuries related to a device (21 USC 360i(b)(5)). The legislation did not otherwise specify the characteristics of this new system, which, when fully implemented by regulation, is to replace the existing requirements applicable to all user facilities.

Prior to the 1997 legislation, FDA had already begun work on a sentinel surveillance system based on an analysis of problems with the existing reporting system. It launched an initial pilot study (Devicenet) that involved some 23 health care facilities in the Washington/Baltimore and Raleigh/Durham areas plus one Boston hospital (Gardner and Flack, 1999). In a second phase starting in 2002, FDA began to recruit a larger number of facilities, primarily from the East Coast. By the end of 2004, recruitment had extended to the West Coast, and more than 300 facilities were participating (FDA, 2004b; personal communication, Marilyn Flack, M.A., Policy Analyst, CDRH, January 3, 2005). This expanded system is known as the Medical Product Surveillance Network or MedSun.

MedSun participants agree to submit both mandatory and voluntary user facility reports. If participants submit an adverse event report that is mandated under current regulations, MedSun staff forward the report to the manufacturer. For voluntary reports (e.g., "close calls" that do not result in harm), participants can tell MedSun staff whether they want such reports to be forwarded or not (although FDA encourages such forwarding).

After FDA has gained extensive experience with MedSun and before writing new regulations for user facility reporting, the agency will evaluate the program to determine which aspects are most useful in promoting reliable, accurate reporting of adverse device events. The pilot program is discussed further in Chapter 4.

Required Postmarket Surveillance Studies and Condition-of-Approval Studies

As discussed in Chapter 1, Section 522 of the Federal Food, Drug, and Cosmetic Act uses the term *Postmarket Surveillance* to describe one type of surveillance, specifically, studies and other information collection that FDA may require manufacturers to undertake to gather additional safety and efficacy data for a small group of Class II and Class III devices (21 CFR 822). As originally provided for in the Safe Medical Devices Act of 1990, such surveillance was required for devices introduced into interstate commerce after January 1, 1991, that were (1) permanent implants that could cause serious adverse outcomes or death if they failed, (2) devices intended for use in supporting or sustaining human life, or (3) devices that presented a potential serious risk to human health. The legislation also provided that FDA could require this kind of Postmarket Surveillance for other devices, regardless of the date introduced to the market, if FDA deemed it necessary to protect the public health.

The FDA Modernization Act of 1997 eliminated the provisions for required Section 522 Postmarket Surveillance. Instead, it gave FDA the discretion to order studies or other information collection for any Class II or Class III device that (1) would be reasonably likely to have serious adverse health consequences if it failed; (2) is intended for implantation for more than 1 year; or (3) is intended to be life sustaining or life supporting and to be used outside a health care ("device user") facility. Devices in the last category include those intended to be used at home. The legislation also provided for greater latitude in the methods that could be used in undertaking this kind of surveillance activity. According to FDA guidance, approaches might include a review of scientific literature, analysis of secondary datasets (e.g., Medicare data), nonclinical testing of a device, analysis of a manufacturer's complaint file for a device, and various types of experimental or observational studies (FDA, 1998g).

In 1998, FDA announced the end of mandatory Postmarket Surveillance for several device categories, including pacemakers (generators), replacement heart valves, and coronary vascular stents (FDA, 1998e). Requirements continued for several other devices, including silicone breast implants, pacemaker leads, and temporomandibular joint prostheses. According to FDA staff, only two Section 522 Postmarket Surveillance studies have been ordered since the 1997 legislation (Tillman and Gardner, 2004). (See Chapter 5 for further discussion of these studies.)

As described by FDA, the primary objective of this particular type of surveillance "is to study the performance of the device after marketing as it is to be used in the general population for which it is intended . . . [with a focus on] morbidity or mortality . . . [and on] device failure and its atten-

dant impact on the patient" (FDA, 1998b, unpaged). The criteria FDA considers in determining whether to order this kind of surveillance include the existence of an important unanswered surveillance question (e.g., how well home users of a device retain training for devices that have moved from professional to home use), the potential for other postmarket tools to answer the question, significance of the risk to public health related to the question, and the feasibility of a study (FDA, 1998g). Manufacturers ordered to conduct a Section 522 Postmarket Surveillance study must submit a surveillance plan for approval within 30 days of receiving the order.

Section 522 studies are not explicitly required to have IRB approval or informed consent (in contrast to IDE investigations, which are covered by Section 520(g). Although FDA regulations do not mention IRB review and approval of postmarket clinical studies, they do not explicitly exclude them from such requirements (21 CFR 56.104). FDA has said that its review of a manufacturer's plans for required postmarket surveillance would consider whether appropriate patient protections are needed and included (FDA, 2002o). Depending on the specifics of the surveillance plan, other federal regulations or research institution policies may require IRB review even if FDA does not.

As noted above, only two Section 522 studies have been ordered in recent years. More common are study requirements imposed at the time a PMA application is approved. Although these condition-of-approval studies necessarily take place after a device has entered the market, the studies traditionally have not been considered part of the postmarket surveillance program. Recently, however, the agency shifted responsibility for monitoring and evaluating these studies from the Office of Device Evaluation to the Office of Surveillance and Biometrics.

Medical Device Tracking

The tracking of medical devices is intended to assist the prompt notification of users when a device presents a serious, immediate risk to health and to speed the recall of such a device when appropriate. The Safe Medical Devices Act of 1990 required that certain medical devices (those with the same characteristics as those for which the legislation required postmarket surveillance studies) be tracked so their location could be determined if needed. The FDA Modernization Act of 1997 made tracking of such devices discretionary. In the following 2 years, FDA rescinded dozens of mandatory device tracking orders across several product categories (FDA, 1998a).

In considering whether to issue a tracking order, FDA may consider the likelihood that a device will experience a sudden, catastrophic failure; the potential for a significant adverse health outcome in the event of such a

failure; and the potential need for prompt professional intervention in such a situation (FDA, 2003j). Such orders may apply to devices already on the market or to newly cleared or approved devices. FDA now requires tracking for 12 implantable devices, including temporomandibular joint prostheses, implantable pacemaker pulse generators, mechanical heart valves, and implantable infusion pumps (FDA, 2003j). It also has required tracking for four devices used outside hospitals and similar facilities. The requirement covers ventricular bypass assist devices, breathing frequency monitors, continuous ventilators, and direct-current defibrillators and paddles.

Manufacturers should be able to provide key information to FDA about the location of a tracked device within 10 working days for devices that have already been distributed to patients and within 3 days for those that have not. For tracked devices not intended for reuse, required information includes the name and contact information for the patient, the prescribing physician, the physician who is following the patient, and all distributors of the device. For a device intended for reuse, the manufacturer must be able to provide information about the distributor, the patient currently using the device (if available), the prescribing physician, and the date the device is returned to the manufacturer, destroyed, retired from use, or remarketed. Tracking continues for the life of the device, unless FDA rescinds the tracking order. Device distributors, including hospitals and physicians that supply tracked devices to patients, must make their tracking records available to manufacturers when requested. Patient consent for tracking is not required, but patients may refuse to provide or authorize release of their personal information for purposes of having their device tracked.

RESPONSES TO POTENTIAL SAFETY PROBLEMS

When it is reasonably clear that a problem exists, understanding that problem and evaluating an appropriate response may take considerable analysis. For example, after a 6-year-old boy suffered fatal skull injuries when a magnetic resonance imaging (MRI) scanner pulled an oxygen device into the scanner's magnetic field, what is now the Office of Science and Engineering Laboratories studied the effects of large magnetic fields on such devices and found that effects were too inconsistent to support general conclusions (OST, 2002). The broader problem of MRI magnetization of nearby metal items, including certain implanted medical devices, has been recognized by FDA, clinicians, and manufacturers for many years (FDA, 2001k). Various groups, including FDA, ECRI, American College of Radiology, and International Electrotechnical Commission (which publishes international standards for electrical, electronic, and related technologies) have issued safety guidance and standards for MRI use.

FDA and manufacturers have several options in responding to an identified safety problem. Responses may differ depending on whether the problem is newly recognized or already known.

Recalls and Corrections

Once a manufacturer or FDA concludes that a problem with a device exists, several steps are possible. At one extreme, a manufacturer may recall all units of a device and cease manufacturing it temporarily or permanently. For example, after a children's hospital reported a number of infections following use of a device for detecting carbon dioxide in tissues and then identified an infectious agent in the saline packaging for the device, the manufacturer issued a voluntary recall of the device and ceased production pending determination of the source of the contamination problem (Tyco, 2004; also FDA, 2004u).

To cite another example, a manufacturer of a disposable blood pressure cuff for neonates recalled some 26,000 units after problems were noted with the inflatable portion of the cuff (FDA, 2004g). Subsequently, after FDA noted deficiencies in good manufacturing practices, the company initiated another recall of more than 220,000 units (FDA, 2004f). Recalls may involve only certain specific lots or units, for example, units that were affected by a transient and since-corrected manufacturing problem.

One recent recall involved only the revised instructions for use of a stent that had been cleared for treatment of certain bile duct obstructions (Cordis, 2004). The recall was based on two concerns: first, the revised instructions involved indications for vascular use that had not been cleared by FDA, and second, several injuries and malfunctions had been reported with use of the device outside of the approved indications (FDA, 2004s).

Recalls may be undertaken at a manufacturer's own initiative, as a result of an FDA request, or—rarely—after an FDA order. The agency almost always relies on voluntary manufacturer action to recall hazardous products. Voluntary device recalls not undertaken at the request of FDA must be reported to the agency if they meet certain requirements specified in the regulations (21 CFR Part 806.10) (see Class I or Class II recalls, as defined below). FDA has the statutory authority to order a recall of a medical device under very restricted circumstances—only after a finding that there is a reasonable probability that a device "would cause serious, adverse health consequences or death" and when certain other conditions are met (e.g., a company refuses to recall a product voluntarily following an agency request (21 CFR 810.10).

FDA guidelines categorize recalls into three classes based on the extent of the hazard (FDA, 2004j). They are

- *Class I recalls* involve dangerous or defective products that have a reasonable probability of causing serious health problems or death. Example: recall of the carbon dioxide sensor described above. Example: recall of a ventilator for a malfunction that might result in overpressure, culminating in serious injury or death in patients whose body weight is less than 20 kilograms (FDA, 2000e).
- *Class II recalls* involve products that might be expected to cause a temporary health problem or that pose only a slight threat of a serious nature. Example: recall of certain unimplanted cochlear implants because of the potential presence of moisture in the internal circuitry of the devices, which could cause loss of function (FDA, 2004i).
- *Class III recalls* involve products that are unlikely to cause any adverse health reaction but that violate FDA labeling or manufacturing regulations. Example: a nephroureteral stent system that was mislabeled as to size (FDA, 2004h).

Depending on the danger involved, FDA may or may not publicize a manufacturer recall beyond including the information in its list of enforcement actions (which can be found at http://www.fda.gov/po/enforceindex/2004enforce.html). Likewise, the intensity of FDA monitoring of the recall process varies depending on the risk presented by the device problem (Blevins, 2003). Recently, FDA began issuing press releases for all Class I recalls (personal communication, Thomas P. Gross, M.D., Director, Division of Postmarket Surveillance, CDRH, May 13, 2005).

Rather than seeking the physical removal of a device from user facilities (or from patients, in the case of some implants), a manufacturer may institute a correction, a type of recall that involves the "repair, modification, adjustment, relabeling, destruction, or inspection (including patient monitoring) of a product without its physical removal to some other location" (FDA, 2002i, unpaged).[16] A correction might involve a manufacturer representative visiting affected facilities and replacing or otherwise fixing a malfunctioning device. A corrective action, in contrast, is intended to eliminate the basic cause of the problem, for example, through redesign of a device.

[16]FDA's MedWatch website lists safety-related changes in labeling for drugs but not for devices (see FDA, 2005d). To cite a well-publicized example, in March 2004 FDA issued a public health advisory that asked manufacturers to change the labels of several antidepressant drugs to warn physicians to monitor patients for worsening of depression and evidence of suicidal thoughts or behavior (FDA, 2004l; see also FDA, 2004k).

Public Health Notifications

For many device-related problems, a less dramatic response than a recall is appropriate. One option is for FDA to issue a Public Health Notification, a term that FDA has recently decided to apply comprehensively to what had been distinguished as Safety Alerts, Public Health Notifications, and Public Health Advisories (Schultz, 2004). (All notifications since 1983 are provided or listed at http://www.fda.gov/cdrh/safety.html#web).

The information provided in Public Health Notifications is quite varied. Some notifications involve individual products (e.g., a particular brand of drug-eluting stent), whereas others concern a general type of product (e.g., hospital beds). Notifications may discuss newly identified problems (e.g., the notification about meningitis linked to cochlear implants, which included recommendations for recognizing the condition, treating it, and vaccinating to prevent it (Pressly, 2003)). As discussed below, notifications may also provide safety tips or information related to previously recognized problems.

Information included in a Public Health Notification may be disseminated to user facilities, health professionals, health educators, and consumers in various ways designed to fit the topic and the audiences. Methods include letters, e-mail notifications, items in FDA electronic newsletters, posting on various FDA webpages, press releases, articles and other communications in professional journals, and conference and other presentations.

Consistent with FDA requirements, manufacturers likewise may use a number of strategies for alerting user facilities, professionals, or consumers about device problems, including phone calls and certified letters. For notifications that do not involve company-initiated recalls and other actions, FDA does not require companies to disclose the existence of a Public Health Notification about their product, although they may do so voluntarily.

Device Redesign and Preventive Design

Again, depending on the nature of an identified problem and discussions with FDA and others, a manufacturer may respond to a problem by modifying the design of a device (e.g., relocating or shielding a switch, discontinuing the use of a troublesome material) or changing the manufacturing process (e.g., redesigning sterilization procedures). Analyses undertaken by FDA of data on device recalls from 1983 to 1989 found that more than 40 percent of the quality problems that prompted recalls could be traced to product design deficiencies (FDA, 1990). That same year, another study conducted by the Inspector General of the Department of Health and Human Services reached similar conclusions (OIG, 1991).

Depending on initial information, FDA staff may become involved in

analyses of the design of devices associated with multiple adverse event reports. Examples include glucose meters, infant apnea monitors, ventilators, and infusion devices (Wiklund, 2003). Although not expressed in terms of design changes per se, in 2002 FDA issued a guidance document for apnea monitors that identified risks to health associated with the monitors and recommended device features or testing procedures to mitigate each risk (FDA, 2002c).

In addition to considering whether design problems have contributed to reported adverse events, FDA also seeks to prevent safety problems related to design deficiencies. Quality system regulations, which apply to the development and manufacture of devices (and, thus, apply both before and after a device is marketed), emphasize the detection and correction of problems during the manufacturing process. The goal is to prevent the problems that would trigger a recall or Public Health Notification.[17]

Responses to Familiar Problems

As noted above, the focus of adverse event reporting and other postmarket surveillance activities is on the detection of unexpected, serious problems or recognized problems occurring more frequently than expected. Sometimes, however, the agency targets familiar, well-recognized problems for special initiatives and collaborations with other public and private groups.

For example, in 2001, FDA issued a notice on reducing the radiation risk from computed tomography for pediatric and small adult patients (Feigal, 2001b). The agency acknowledged that the recommendations were not new, but it decided it was important to emphasize that radiation doses for small patients should be kept as low as possible, consistent with achieving clinical objectives.

On another front, FDA has created a home health care committee to review what FDA has done and might do to respond to problems with the use of complex medical devices in the home (see, FDA, 2004c). The agency has recognized that the use of sophisticated medical devices in the home, while an accepted and necessary part of modern health care, "adds an additional level of risk of unintended adverse events" (Arcarese, 2002a, unpaged). Based on discussions with a range of interested parties, the home health committee has decided to focus in particular on safe use of infusion pumps in the home. It

[17]The relevance of design controls to the prevention of safety problems is suggested by this FDA description of what might be required of a manufacturer planning a new defibrillator for use by hospital and emergency medical personnel. "Designers would have to consider all aspects of use in both settings . . . [including] storage temperatures in the ambulance, road shock and vibration, two-way radio interference, electrical noise generated by the siren and many other factors" (FDA, 1996a, unpaged).

has asked pump manufacturers to provide basic information and use instruction for every infusion pump marketed since 1984. The information will be included on the committee's website to allow ready access to such information by patients, family members, and home care nurses.[18]

CONFIDENTIALITY OF INFORMATION OBTAINED BY FDA

Much information that FDA receives is confidential or is treated as confidential. The scope of agency confidentiality requirements or practices has been a prominent focus of criticism during recent controversies about the availability of information from postmarket studies of drugs. As discussed in Chapters 5 and 6, the committee's efforts to learn more about the status or findings of postmarket studies ordered by FDA were limited by agency confidentiality policies (as well as by the agency's lack of an adequate study monitoring system).

Confidentiality protections for information submitted to FDA are provided by three key federal statutes: the Federal Food, Drug, and Cosmetic Act (21 USC 301 et seq.), the Freedom of Information Act (5 USC 552), and the Trade Secrets Act (18 USC 1905). Implementing regulations clarify how these protections apply to study protocols and to preclinical and clinical study data, as well as to information relating to product design, product composition, and manufacturing methods and processes. Confidentiality provisions of the Privacy Act (5 USC 552a) also restrict the disclosure of information about individuals, including patients and health care personnel. Confidential information can, of course, be leaked or released mistakenly, but the provisions described here normally operate as intended to restrict disclosure of covered categories of information.

FDA personnel are prohibited from disclosing (or from using to their own advantage) information acquired under their statutory authority that concerns "any method or process which as a trade secret is entitled to protection"[19] (21 USC 331(j)). This provision covers information acquired by FDA under investigational device exemption applications, 510(k) premarket notifications, and premarket approval applications, or otherwise acquired under authority of various statutory provisions. The provision does not expressly include Section 522, which authorizes FDA to require

[18]The home care committee has already issued a pamphlet for consumers on blood glucose monitors and prepared a checklist for consumers to promote safe use of devices in the home (FDA, 2003m).

[19]This provision does not authorize the withholding of information from the U.S. House of Representatives, Senate, or a committee or subcommittee thereof with jurisdiction over the specific subject matter.

postmarket surveillance and requires a manufacturer to submit a plan for the required surveillance (21 USC 360(l)). FDA, however, treats such plans as protected from public disclosure under provisions of the Freedom of Information Act and FDA's implementing regulations. Interim and final reports of postmarket surveillance studies or data are treated similarly, although limited findings may be made public in connection with a safety advisory, the approval of a new indication for a product's use, a labeling change, or similar action. Data and information relating to postmarket studies conducted under an IDE would be protected consistent with the IDE confidentiality regulations.

More broadly, the federal Trade Secrets Act prohibits federal employees from disclosing information which "concerns or relates to the trade secrets, processes, operations, style of work, or apparatus or to the identity, confidential statistical data, amount or source of any income" or other financial information of any person or company (18 USC 1905). The Trade Secrets Act is a criminal statute. Likewise, a violation of disclosure provisions of the FDA statute (21 USC 331(j)) is subject to criminal penalties (21 USC 333(a)). Congress can, however, request or subpoena information including trade secret and confidential commercial information, and that is not subject to 331(j) nondisclosure.

In addition, FDA can require that a summary of safety and effectiveness information be submitted to document the basis for premarket approval, and the agency can release the summary to the public once it has issued an approval order. Such a summary "shall include information respecting any adverse effect on health of the device" (21 USC 360j(h)(2)). Much of the committee's understanding of the kinds of studies submitted to support PMA approvals was obtained by reading individual approval summaries, which are posted on the CDRH website.

Otherwise, by statute, information contained in a PMA application is to be held confidential and is not to be used by FDA to approve another manufacturer's PMA application, to establish a performance standard or special control, to reclassify a device, or to approve a product development protocol (21 USC 360j(c)). An exception is that information from preclinical or clinical tests or studies that demonstrate safety or effectiveness can be used by FDA for these purposes 6 years after the approval of the PMA application, but this exception does not cover information regarding "methods of manufacture and product composition and other trade secrets" (21 USC 360(j)(h)(4)).

An FDA regulation provides confidentiality protections for PMA filings (21 CFR 814.9). It provides that the existence of a PMA filing will not be disclosed by FDA if its existence has not been disclosed by the applicant, up until the time the PMA application is approved or denied approval. An exception permits FDA to disclose a summary of portions of the safety and

effectiveness data prior to approval "if disclosure is relevant to public consideration of a specific pending issue" (21 CFR 814.9(d)(1)). After approval, FDA can disclose certain information in the PMA application, except for trade secret or confidential commercial information. FDA can disclose: (1) safety and effectiveness data "previously disclosed to the public"; (2) a protocol for a test or study "unless the protocol is shown to constitute trade secret or confidential commercial or financial information" protected under the Freedom of Information Act and implementing regulations; (3) adverse reaction reports, consumer complaints, and similar data and information—but only after deleting trade secret or confidential commercial or financial information and deleting personnel, medical, and similar information the disclosure of which would constitute an unwarranted invasion of personal privacy; (4) assay methods and other analytical methods, unless they do not serve a regulatory purpose and they are trade secret or confidential commercial information; and (5) a list of components previously disclosed to the public. FDA cannot disclose: (1) safety and effectiveness information not previously disclosed to the public that constitute trade secret or confidential commercial information; (2) manufacturing methods or processes, including quality control procedures; (3) quantitative or semiquantitative formulas; and (4) production, sales, distribution, and other similar data and information.

Data and information contained in an IDE is handled in accordance with the PMA regulation in Section 814.9 (21 CFR 812.38(d)). Similar confidentiality provisions apply to data and information contained in a 510(k) notification and disclosure of the existence of a 510(k) notification prior to its clearance (21 CFR 807.95). An exception exists under all these regulations that permits FDA to disclose a summary of portions of the safety and effectiveness data prior to approval or clearance "if disclosure is relevant to public consideration of a specific pending issue."

The Freedom of Information Act directs federal agencies to make information in agency files available to the public, but certain information is exempted from public disclosure. Among the types of exempted information are (1) "trade secrets and commercial or financial information obtained from a person and privileged or confidential," (2) "personnel and medical files and similar files the disclosure of which would constitute a clearly unwarranted invasion of personal privacy," and (3) information specifically exempted from disclosure by statute (5 USC 552(b)(3), (4), and (6)). FDA has issued regulations implementing these exemptions. Under the regulation applicable to trade secrets and confidential commercial information (21 CFR 20.61), FDA has defined these terms as follows:

> (a) A trade secret may consist of any commercially valuable plan, formula, process, or device that is used for the making, preparing, com-

> pounding, or processing of trade commodities and that can be said to be the end product of either innovation or substantial effort. There must be a direct relationship between the trade secret and the productive process.
>
> (b) Commercial or financial information that is privileged or confidential means valuable data or information which is used in one's business and is of a type customarily held in strict confidence or regarded as privileged and not disclosed to any member of the public by the person to whom it belongs.

FDA's regulation applicable to medical information provides that names and "information which would identify patients or research subjects in any medical or similar report, test, study or other research project" shall be deleted prior to public disclosure of the record (21 CFR 20.63(a)). "The names and any information that would identify the voluntary reporter or any other person associated with an adverse event" shall not be publicly disclosed by FDA or by a manufacturer who reports such an event (21 CFR 20.63(f)). The names of entities required by statute to make adverse event reports are not protected from disclosure.

FDA's definitions of trade secret and confidential commercial information were drafted to be consistent with judicial determinations that "any technical or scientific information developed by a company may be considered a trade secret where it is not generally known or readily ascertainable and when it is protected and maintained as confidential by the developer and is of value to him" (FDA, 1974, p. 44613). Testing data, including protocols used for testing the product and test results, can be protected from disclosure under the Freedom of Information Act (e.g., Heeney v. FDA, 2001).

Sometimes other statutes may affect the confidentiality protections usually afforded to confidential commercial or financial information under the Federal Food, Drug, and Cosmetic Act and the Freedom of Information Act. For example, public companies subject to regulation by the Securities and Exchange Commission (SEC) are required to disclose certain information that might be "material" to decisions by investors and potential investors. To comply with these SEC requirements, a public company might publicly disclose in SEC filings or press releases certain information about the existence of a clinical trial, the results of a clinical or preclinical study, or the fact that a PMA application or 510(k) submission has been submitted to FDA. Companies that are privately funded (such as by venture capital or private investors) might not disclose such information if they are not subject to disclosure requirements. As discussed above, FDA is bound by confidentiality requirements to the extent the information has not been previously disclosed to the public.

Companies provide the highest confidentiality protections to device design information, manufacturing processes and methods, and quality con-

trol information. Protocols for clinical studies and preclinical testing are also typically protected from public disclosure. Aggregate results of a safety and effectiveness study may be disclosed in summary form, but raw data or site-specific data are often protected as confidential, unless published in a scientific journal.

As applied in the context of postmarket surveillance, FDA would be required by the three statutes discussed above to protect from public disclosure information that constitutes trade secrets or confidential commercial information. For example, a postmarket study protocol and the results of condition-of-approval studies would be submitted as supplemental PMA applications and thus would be governed by the confidentiality requirements of the Federal Food, Drug, and Cosmetic Act and Section 814.9 of FDA's regulations.

Under the postmarket surveillance provision in Section 522 of the Act, a manufacturer is required to submit a plan for FDA-required postmarket surveillance, but FDA treats such plans as protected from public disclosure under provisions of the Freedom of Information Act and FDA's implementing regulations. Interim and final reports of postmarket surveillance studies or data are treated similarly, although limited findings may be made public in connection with a safety advisory, the approval of a new indication for a product's use, a labeling change, or similar action. Data and information relating to postmarket studies conducted under an IDE would be protected consistent with the IDE confidentiality regulations.

FDA PROGRAMS THAT CROSS THE PREMARKET/POSTMARKET BOUNDARY

In addition to premarket and postmarket programs, FDA has programs that cross the market approval boundary to promote device safety both before and after a device is marketed. This is consistent with the agency's analysis of its range of activities as they relate to a product's total life cycle from initial concept to obsolescence (see Figure 1.2).

Research, Analysis, and Methods Development

As described above, CDRH has active research programs to evaluate elements of device technologies or their effects, to support the development of standards or guidance, and otherwise to build the knowledge base for device design, testing, manufacture, regulation, and clinical use. CDRH's 2003 Annual Report described its epidemiological research program, which provides consultative services on topics or problems requiring epidemiological expertise (e.g., literature reviews, risk assessments, design of obser-

vational studies). The report listed studies that produced journal publications and conference presentations on a broad range of topics, including allergic reactions to platinum in breast implants, breast implant rupture, tampon-associated toxic shock syndrome, gender differences in pulmonary artery rupture, and uses and outcomes associated with transmyocardial revascularization (a procedure sometimes used to relieve chest pain). Other studies focused on methodology or process issues, for example, the use of the National Electronic Injury Surveillance System (NEISS) to assess the frequency of injuries due to medical devices. CDRH epidemiologists have also participated, on an exploratory basis, in premarket approval assessments to help determine whether and what kind of postmarket evaluations would be appropriate.

Concern about deficiencies in device design has prompted FDA to direct more attention to general principles and strategies for safe device design and use, including human factors engineering. Human factors engineering analyzes how people employ technologies and how user characteristics (e.g., cognitive capacities, expectations) interact with characteristics of their environments (e.g., workload, lighting) to affect the safe and effective use of technologies (FDA, 2003s). Such analysis can be applied to adverse events involving medical devices and potential means to prevent them.

Quality Systems Regulations

A major boundary crossing program involves quality system regulations, which encompass good manufacturing practices. These regulations are among the general controls described earlier in this chapter.

Congressional concern about manufacturing practices dates back at least to the 1938 Federal Food, Drug, and Cosmetic Act, when Congress specified that manufacturing methods, facilities, and controls be "adequate" for regulated products. The first FDA guidance about adequate manufacturing processes dates to the early 1940s; it followed a drug manufacturing mishap that left dozens of people dead or injured (Swann, 1999).

FDA issued the first requirements for good manufacturing practices for medical devices in 1978 (FDA, 1978). These requirements—which remained essentially the same until 1996—covered methods, facilities and controls related to the manufacture, packing, storage, and installation of medical devices. The Safe Medical Devices Act of 1990 expanded FDA authority to include control related to device design prior to actual production. That legislation also encouraged FDA to work with other countries toward commonly recognized good manufacturing practices.

In 1996, FDA published the Quality System Regulations, which it described as "revising the current good manufacturing practice (CGMP) requirements for medical devices and incorporating them into a quality sys-

tem regulation" (FDA, 1996b, p. 52602). By intent, the regulations are very similar to the International Organization for Standardization (ISO) provisions (ISO, 2000), which have recently been updated. (ISO is described briefly below.) The quality system regulation is broad in scope as indicated in Box 3.4.

The quality system regulations cover a very large array of devices. For that reason, the regulation "provides the framework that all manufacturers must follow by requiring that manufacturers develop and follow procedures and fill in the details that are appropriate to a given device according to the current state-of-the-art manufacturing for that specific device" (FDA, 1996b, p. 52603). As noted earlier, special control guidance documents for particular categories of devices (e.g., apnea monitors) may be much more specific.

BOX 3.4
Topics in *Medical Device Quality Systems Manual: A Small Entity Compliance Guide*

1. The Quality System Regulation
2. Quality Systems
3. Design Controls
4. Process Validation
5. Personnel
6. Buildings and Environment
7. Equipment and Calibration
8. Device Master Record
9. Document and Change Control
10. Purchasing and Acceptance Activities
11. Labeling
12. Product Evaluation
13. Packaging
14. Storage, Distribution, and Installation
15. Complaints
16. Servicing
17. Quality Systems Audits
18. Factory Inspections
19. Appendix
    Appendix 1: The Quality Systems Regulation
    Appendix 2: Application of the Medical Device GMPs [Good Manufacturing Practice] to Computerized Devices and Manufacturing Processes

SOURCE: FDA, 1999c.

Design Controls

As described in the quality system regulations (21 CFR 820.30), the design controls requirements for Class II and III devices, Class II and III investigational devices, and certain Class I devices cover considerable ground. Design controls involve

- creating plans that cover design and development activities and assign responsibility for implementing them;
- specifying design input requirements, that is, the physical and performance requirements for a device design that are appropriate given the device's intended uses and users;
- developing the design output, meaning the results of the design effort at each stage, including the finished design effort (the device, its packaging and labeling, and the device master record);
- verifying that the design output is consistent with the design input requirements;
- conducting periodic design reviews to assess the adequacy of the design requirements, evaluate whether the design will meet the requirements, and identify problems;
- validating through tests of production units under actual or simulated conditions and other means that the device (including software) meets objectives for intended uses and users;
- correctly translating the device design into production specifications;
- controlling changes in design during the design process and after the device is marketed; and
- documenting the design process in the design history file.

FDA requires that applications for premarket approval include descriptions of design controls and other quality systems information, and it evaluates compliance during a pre-approval facility inspection (FDA, 2003q,r). The agency also evaluates compliance during routine quality systems inspections for all devices covered by the design control requirements.

Corrective and Preventive Actions

In guidance on the quality system inspections of manufacturers, one focus is what FDA terms the Corrective and Preventive Actions or CAPA subsystem (FDA, 1999b). A major component of this subsystem consists of procedures to detect, understand, and correct problems during the manufacturing process. The objective of this aspect of quality system regulations is to prevent defective devices from reaching the market. Other components of the CAPA subsystem reviewed by FDA are the manufacturer's confor-

mance with adverse event reporting regulations, recall and corrective actions, and procedures for any required tracking of a medical device.

Inspections

As noted above, FDA inspections of manufacturing facilities may occur before or after a medical device is approved for marketing. A pre-approval inspection is usually required as part of the PMA process. FDA staff also conduct "directed" or "for cause" inspections when they are investigating a specific problem or following up to assure that corrective actions from a previous inspection have been implemented. A program of bioresearch monitoring includes on-site inspections and data audits of sites involved in FDA-regulated research. As described by FDA in its 2002 Performance Plan, the FDA Modernization Act of 1997 has allowed firms to declare conformity to standards or quality systems requirements as part of steps to streamline the premarket clearance process (FDA, 2001h). This has increased the burden on FDA's inspection process, which as discussed in Chapter 7, falls short of meeting statutory requirements that FDA inspect facilities that manufacture Class II and III devices every 2 years (21 USC 360(h)).

FDA's quality system inspections focus on particular subsystems of manufacturing quality controls, specifically management, design (see above), corrective and preventive actions (see above), and production and processes. The other major subsystems involve materials controls, facility and equipment controls, and records, documents, and change controls.

To ease the inspection burden on FDA, the 2002 Medical Device User Fee and Modernization Act gave manufacturers with a good history of regulatory compliance the option, under certain circumstances, of choosing an FDA-accredited, nongovernmental entity to perform quality systems inspections (21 USC 374(g)). (This is described by FDA as its "Accredited Persons" or AP program.) FDA staff would focus on firms with a record of compliance problems and manufacturers of high-risk products, including implants and life-supporting or sustaining devices.

International Efforts to Harmonize Policies

Medical device development, research, and sales are international in scope. The ISO standards cited above are one example of a number of cross-national initiatives—some longstanding, some relatively recent—to promote consensus and consistency in regulatory and voluntary standards for medical and other products and industries, measurement and testing methods, management systems, and other areas. ISO is a nongovernmental network whose membership consists of the national standards institutes of

nearly 150 countries (ISO, 2004). Using committees that include producers, consumers, regulators, and other relevant parties, the organization develops consensus standards on topics such as terminology, testing methods, product characteristics, and manufacturing processes. Some standards are generic, such as ISO 9000, which concerns quality management. Other standards are industry or product specific, such as ISO 13485, which concerns medical devices. The agency currently has more than 14,000 standards and related documents. Individual countries may choose to adopt the standards by regulation.

In the 1990s, the Global Harmonization Task Force (GHTF) was created specifically as a voluntary process to pursue harmonization of national policies on the regulation of medical devices. It includes participants from national regulatory agencies and industry. Of four GHTF study groups, one has focused on postmarket surveillance, including adverse event reporting programs. FDA supports this activity, but the study group findings and recommendations are advisory, not binding.

One issue for the GHTF task force on adverse event reporting is promoting the exchange of event reports among "national competent authorities" (e.g., FDA in the United States) (GHTF, 2002, p. 4). In 2003, authorities in 16 countries exchanged more than 140 "international vigilance reports," most related to recalled devices (FDA, 2004v).

Other harmonization activities include those of the International Conference on Harmonization (ICH). ICH has, for example, provided guidance for clinical investigators, primarily those involved in drug studies (ICH, 1996). An ISO document has focused on clinical investigators studying medical devices (ISO, 2003a,b; see Giroud, 2004). FDA has not adopted that ISO standard but has said that it might do so after the next revisions (Dickinson, 2004b).

This chapter has focused on description rather than assessment. Thus, it includes no conclusions or recommendations related to the adequacy of existing laws and regulations or their implementation as they relate to children. The next chapter examines FDA's programs of adverse event reporting and offers recommendations for improvement.

4

Identifying and Understanding Adverse Medical Device Events

"The hardest thing over the time that he was growing up—in the first year, mostly—was establishing my credibility with the doctors as a reporter to them. . . . [T]hat was the hardest thing, people not believing . . . that there was something going on and that I wasn't just a hysterical mother."

Nancy Harder, parent, 2004

Communication gaps between patients or parents and physicians are a longstanding concern in medicine and can cause considerable distress to parents. Poor communication can contribute to adverse events or other harms when physicians do not give credence to patient or family reports of problems, as recounted in the quote above from the mother of two children who have spina bifida and rely on cerebrospinal fluid shunts and other medical devices. Inadequate communication can also create problems when patients and family caregivers are inadequately prepared to fulfill their responsibilities for using or maintaining complex medical device. As care has shifted out of the hospital into the home, parents are bringing children home with ventilators, feeding tubes, monitors, and other complex or unfamiliar devices. This is stressful enough without the additional stress of poor training and education about the device use and problem identification. Communication gaps may reflect a physician's lack of awareness of the problems that families and patients face in safely using medical equipment at home.

As emphasized in Chapter 1, the migration of care from hospital to home has brought many benefits, but it also presents risks as parents and families assume responsibilities for device operation, maintenance, and problem recognition once assigned to health care professionals. Surveillance programs, which have other limitations described in this chapter, have yet to adjust to the changed circumstances of much patient care.

The identification, reporting, and analysis of serious adverse device events and device failures and malfunctions are important elements of the

U.S. Food and Drug Administration's (FDA's) overall program of postmarket surveillance. A primary aim of the agency's adverse event reporting program is to identify serious problems with a device (or its use) that become evident after a device is marketed when—depending on the device—it is used with many more patients, with different patient populations (e.g., children), in different ways (e.g., involving ad hoc modifications for pediatric use), for different purposes, in new and possibly less well-equipped settings, over longer periods, and, sometimes, by less experienced or skilled clinicians and care teams. Systematic clinical studies are often a superior tool for assessing these dimensions of device use, but such studies are not realistic for the entire array of devices that enter the market each year. Moreover, just as premarket studies may fail to detect rare events, so may postmarket clinical studies.

Although FDA is most interested in reports of serious unanticipated events, the adverse event reporting program also collects information that can be useful in understanding certain already recognized risks, for example, patient deaths by entrapment in the rails of hospital beds. In addition, reports of device failures and malfunctions—even when they have not caused harm—can help FDA and manufacturers to detect hazards that arise from aberrations in the manufacturing, distribution, modification, maintenance, storage, or reprocessing of a medical device. Adverse event reports can also lead to improvements in the design of a device. For example, in response to problem reports, manufacturers have redesigned cardiac pacemakers to make them substantially less susceptible to electromagnetic interference from modern necessities such as microwave ovens and cellular telephones (Niehaus and Tebbenjohanns, 2001).

For the most part, the public health goals and the limitations of postmarket surveillance policies and programs apply to both adults and children. Systems that support effective postmarket surveillance for patients generally are the foundation on which additions, adaptations, or emphases suited to children's particular needs are then built. For example, the FDA guidance on assessment of pediatric medical devices cited in Chapter 2 makes sense only within an already existing structure for evaluating the safety and effectiveness of medical devices.

The first part of this chapter expands on Chapter 3's description of the FDA program for adverse event reporting. It includes statistics on reports to FDA of adverse device events that involve children and presents examples of actual reports. This discussion is followed by a number of vignettes that illustrate the range of factors and devices that contribute to adverse medical device events with children and the complexities in identifying and understanding these events. Most of the vignettes depict events that result not from single faults or errors but rather from the interplay between weaknesses in some aspect of the design or manufacture of devices and the

circumstances of their use with children. Following the vignettes is a review of the sources of adverse events, the limitations of adverse event reporting, and FDA responses to these limitations. The chapter concludes with recommendations for the FDA.

ADVERSE DEVICE EVENT REPORTING AND FDA

As described in Chapter 3, FDA has authority for two programs of adverse event reporting that involve medical devices. The primary program receives mandatory reports of certain adverse device events from device manufacturers and user facilities and also accepts voluntary reports from health care professionals, consumers, and others. This program is a form of passive surveillance in that it awaits event reports. Active surveillance involves more direct effort by a sponsoring agency to obtain information, for example, through surveys. In addition, based on a sample of user facilities, FDA has created the pilot MedSun program, which includes some elements of active surveillance.

FDA provides Form 3500A (online at http://www.fda.gov/medwatch/getforms.htm) for manufacturers, user facilities, and importers to use for mandatory reporting of serious adverse events and problems involving devices, drugs, and biologics. (Vaccines have a separate reporting system.) The first page of the form asks for information about the

- patient (including age, sex, and weight);
- event or product problem, including an open-ended description of the problem;
- product, including identifying information (e.g., for devices, the brand name, model, manufacturer, model and lot numbers) and other details (e.g., whether a device was an implant and if explanted, whether it is available for examination, and what concomitant medical products or therapies in use);
- outcome (e.g., whether it involved a death or required some kind of intervention); and
- initial reporter (e.g., contact information, whether a health professional).

The second page of the mandatory reporting form requests additional information from user facilities and importers (e.g., where the event occurred, when they became aware of it, who to contact for further information) and manufacturers (e.g., whether they evaluated the device, whether they took any remedial action.

For voluntary reports, FDA provides Form 3500, which has a first page that is almost identical to Form 3500A but has no second page. FDA also offers the option of online reporting for voluntary reporters. The voluntary

reporting form, the online option, and the instructions for reporting clearly require reading skills and knowledge above the levels possessed by many consumers. For example, the form uses terms like "relevant history," "congenital anomaly," "concomitant products," "event abated," and "labeled strength" (FDA, 2003o). The agency urges consumers who want to report an event to have their physician complete the form.

Both mandatory and voluntary reports involving devices are compiled in the Manufacturer and User Facility Device Experience database (MAUDE). After certain information is removed (e.g., patient age, facility name), the reports are made available in a searchable public database. FDA and manufacturers have access to the full reports to support their analyses.

Table 4.1 shows the number of adverse event reports received by FDA from late 1984 to 2004 by major category of reporter, requirement for reporting (mandatory or voluntary), and type of event as designated by the person reporting it. The great majority of reports in MAUDE are submitted by manufacturers. One of the most notable trends shown in the table is the shift of adverse event reports to the alternative summary reporting option after its introduction by FDA in 1995. In recent years, such summary reports have accounted for more than half of total reports, for example, nearly 98,000 of the almost 152,000 reports received in 2004. The sizeable increase in adverse event reports (primarily injuries and malfunctions) from 1992 through 1994 has been attributed, in part, to reports of problems with silicone breast implants, which account for almost one-third of all reports from manufacturers (GAO, 1997).

Mandatory user facility reports account for less than 3 percent of the reports in Table 4.1. This number is, however, somewhat deceptive because FDA attempts to eliminate duplicate reports from the statistics so that a facility report that goes to both FDA and the manufacturer (and then to FDA) is not counted twice. (Facilities are supposed to report to FDA directly only if an event involves a death or the manufacturer of a device is not known.) Voluntary reports from health care professionals and consumers also account for a small percentage of reports (about 3 percent each year).

Unlike some patient safety programs described later in this chapter, FDA does not require or encourage reports of close calls from user facilities. In contrast, manufacturers are required to report device-related malfunctions, including those that *could* cause a death or serious injury if they recurred. When close calls involve situations with the potential to recur and cause harm, reports of such events may provide valuable signals if manufacturer and FDA analysts are prepared to notice them.

FDA sometimes discovers deficiencies in manufacturer reporting of adverse events and product problems (or their systems related to such reporting) during quality systems inspections, through investigations of incidents, and in other ways. The agency typically responds with letters that

TABLE 4.1 Adverse Event Reports Submitted to FDA, Late 1984 Through December 2004

	<1985	1985	1986	1987
Manufacturer reports[a]				
Death	13	585	543	516
Injury	109	9,483	11,738	9,589
Malfunction	28	8,812	7,096	7,596
Other	2	62	10	5
SUBTOTAL	152	18,942	19,387	17,706
User facility reports[b]				
Death				
Injury				
Malfunction				
Other				
SUBTOTAL	0	0	0	0
Distributor and importer reports[c]				
Death				
Injury				
Malfunction				
Other				
SUBTOTAL	0	0	0	0
Voluntary reports[d]				
Death		31	27	21
Injury		345	482	288
Malfunction		520	472	349
Other	22,602	2,097	2,170	1,827
SUBTOTAL	22,602	2,993	3,151	2,485
Summary reports[e]	0	0	0	0
GRAND TOTAL	**22,754**	**21,935**	**22,538**	**20,191**

1988	1989	1990	1991	1992	1993	1994
565	730	951	1,133	1,528	1,339	1,870
8,366	9,845	11,809	18,521	52,894	61,885	79,537
6,677	9,298	16,840	24,796	21,583	45,608	48,629
7	7	4	15	13	38	35
15,615	19,880	29,604	44,465	76,018	108,870	130,071
			7	287	250	266
			2	1,285	1,229	2,338
			6	1,083	988	989
			0	142	337	554
0	0	0	15	2,797	2,804	4,147
				11	18	49
				251	1,103	1,803
				33	139	274
				6	13	121
0	0	0	0	301	1,273	2,247
32	19	319	32	4	5	61
194	364	140	54	77	280	1,292
294	255	252	85	95	167	1,508
1,716	1,664	1,894	3,610	4,439	3,013	2,015
2,236	2,302	2,605	3,781	4,615	3,465	4,876
0	0	0	0	0	0	0
17,851	**22,182**	**32,209**	**48,261**	**83,731**	**116,412**	**141,341**

continued

TABLE 4.1 continued

	1995	1996	1997	1998
Manufacturer reports[a]				
Death	1,773	1,389	1,019	1,021
Injury	51,752	38,236	31,122	18,554
Malfunction	50,125	37,830	32,833	31,960
Other	28	631	2,299	2,485
SUBTOTAL	103,678	78,086	67,273	54,020
User facility reports[b]				
Death	211	346	326	276
Injury	2,315	3,173	3,892	2,556
Malfunction	780	1,091	1,293	860
Other	657	697	657	446
SUBTOTAL	3,963	5,307	6,168	4,138
Distributor and importer reports[c]				
Death	19	27	35	13
Injury	1,661	3,606	1,364	189
Malfunction	164	213	169	289
Other	169	150	70	50
SUBTOTAL	2,013	3,996	1,638	541
Voluntary reports[d]				
Death	73	63	67	75
Injury	1,559	864	835	963
Malfunction	1,367	1,494	1,299	1,523
Other	782	565	405	391
SUBTOTAL	3,781	2,986	2,606	2,952
Summary reports[e]	2,755	6,292	21,682	36,190
GRAND TOTAL	**116,190**	**96,667**	**99,367**	**97,841**

NOTE: Represents most current data (March 31, 2005) for period through December 31, 2004. Yearly report counts are updated periodically to account for delayed data entry issues (e.g., backlog of reports not entered).

[a]Received since December 1984 (MDR Regulation, December 13, 1984).

[b]Received since 1992 (Safe Medical Devices Act of 1990).

[c]Received since 1992 (Safe Medical Devices Act of 1990). Distributors reported since Decem-

1999	2000	2001	2002	2003	2004	TOTAL
905	1,017	1,366	1,266	1,466	1,879	22,874
13,073	13,646	17,354	17,955	18,832	22,769	517,069
29,199	27,683	29,418	36,988	37,270	18,563	528,832
3,140	3,132	2,960	3,544	4,222	3,645	26,284
46,317	45,478	51,098	59,753	61,790	46,856	1,095,059
233	211	240	200	200	217	3,267
1,777	1,568	1,625	1,448	1,156	1,034	25,398
738	654	675	729	1,146	1,405	12,437
264	323	274	303	362	460	5,476
3,012	2,756	2,814	2,680	2,864	3,116	46,581
11	11	9	7	1	3	214
85	55	142	117	198	255	10,829
711	536	206	313	701	184	3,932
78	619	210	297	95	56	1,934
885	1,221	567	734	995	498	16,909
54	92	102	104	153	115	1,449
899	1,397	1,223	1,246	1,200	1,299	15,001
1,416	1,245	1,513	1,773	1,820	1,759	19,206
319	373	411	522	587	538	51,940
2,688	3,107	3,249	3,645	3,760	3,711	87,596
36,969	46,075	65,818	79,189	91,192	97,698	483,860
89,871	**98,637**	**123,546**	**146,001**	**160,601**	**151,879**	**1,730,005**

ber 19, 1998 (FDA Modernization Act of 1997).

[d]Received from 1973 to 1992 (Medical Device Laboratory Product Problem Reporting Program) and 1992 to present (MedWatch).

[e]Received from manufacturers that have been granted exemptions (beginning 1995) from reporting individual adverse events.

SOURCE: Division of Surveillance Systems, FDA Center for Devices and Radiological Health.

outline the problems and needed corrections. Only rarely are criminal penalties sought.[1] FDA staff could not cite cases in which user facilities had been penalized for failure to comply with their mandatory reporting obligations (personal communication, Thomas P. Gross, M.D., Director, Division of Postmarket Surveillance, CDRH, January 28, 2005).

Table 4.2 shows the number of reports submitted that identified adverse events as involving patients under age 21. (These data were supplied by FDA from their internal database. As noted above and in Chapter 3, the public database does not include information on age or birth date.) The table shows no entries for the summary reporting option because this option does not require information on patient age.

The numbers presented in Table 4.2 are undoubtedly an undercount of all *reported* events that involved children (leaving aside all actual events). The fields on the reporting form that request birth date or age information are sometimes not completed, perhaps because the information is not immediately available to the reporter. In FDA's analysis of reports of patient entanglement in hospital bed side rails—an event associated with high rates of death (65 percent of reports) and injury (23 percent of reports)—age was not included for 36 of 111 of the reports in MAUDE (Todd et al., 1997a,b). Of the 75 cases for which age data were provided, 5 percent involved patients under age 17. Even if event reporting were more complete, it would be difficult to assess the extent of a problem without knowing the population at risk (the denominator problem as discussed elsewhere in this report and in Appendix D).

Box 4.1 presents several excerpts from reports to FDA of adverse events that involved children. The examples (which include the full narrative text of the reports) illustrate that reports vary greatly in the amount and usefulness of the information provided. Some offer a relatively clear picture of an event; others are incomplete. Reports nearly always focus on the immediate circumstances surrounding an event and thus are limited in the extent to which they point to contributing system factors, for example, understaffing.

These examples of reports make evident some of the challenges in investigating adverse event reports, especially when the investigator is organizationally removed from the event, as is usually the case for manufacturer or FDA staff. For example, although manufacturers (and FDA) can often follow up with reporters to collect additional information, manufacturers may not have access to the device for inspection, and important information

[1]To cite one noteworthy exception, in 2003, Endovascular Technologies, a subsidiary of a major device manufacturing company, entered guilty pleas on 10 felony charges involving failure to submit problem reports to FDA and paid more than $92 million in civil and criminal penalties to settle the case (Bren, 2003; Hilzenrath, 2003; Jacobs, 2003; Ostrov et al., 2003). The unit admitted to failing to report 2,600 incidents of serious adverse events (including 12 unreported deaths and 57 unreported emergency surgeries) or malfunctions between 1999 and 2001. Instead, it reported only 172 malfunctions. FDA learned of the suppressed reports through an anonymous letter from concerned company employees.

TABLE 4.2 FDA Adverse Event Reports Involving Individuals Under Age 21 (1999–2004)[a]

	1999	2000	2001	2002	2003	2004	TOTAL
Manufacturer							
Death	29	39	94	101	96	92	451
Injury	513	483	838	948	1,040	1,371	5,193
Malfunction	523	540	795	1,279	980	438	4,555
Other	185	162	195	147	173	190	1,052
SUBTOTAL	1,250	1,224	1,922	2,475	2,289	2,091	11,251
User Facility							
Death	17	10	23	19	14	12	95
Injury	134	131	172	107	76	78	698
Malfunction	69	41	61	48	70	64	353
Other	28	17	22	32	39	32	170
SUBTOTAL	248	199	278	206	199	186	1,316
Importer							
Death	0	1	1	0	0	0	2
Injury	7	1	10	43	53	24	138
Malfunction	11	3	13	73	115	42	257
Other	4	19	6	8	2	0	39
SUBTOTAL	22	24	30	124	170	66	436
Voluntary							
Death	7	9	9	15	12	15	67
Injury	86	86	111	141	115	144	683
Malfunction	84	70	133	135	138	156	716
Other	25	31	27	35	38	26	182
SUBTOTAL	202	196	280	326	303	341	1,648
GRAND TOTAL	1,722	1,643	2,510	3,131	2,961	2,684	14,651

[a]Not all reports include information on patient age.
SOURCE: Division of Surveillance Systems, CDRH.

about the device (e.g., brand and model number and even manufacturer) may not have been documented. A later section of this chapter returns to these and other limitations of adverse event reporting programs.

When FDA receives an adverse event or device malfunction report from a manufacturer or other party, it (actually a contractor) checks the report, codes certain information if it has not been coded already by the reporter, and enters the report into the database.[2] FDA has developed codes for both clinical outcomes (e.g., cerebral hemorrhage) and device outcomes (e.g.,

[2]The description of the event review process and the discussion of analysis priorities are based on an April 15, 2004, presentation to the committee by Thomas P. Gross, M.D., Director, Division of Postmarket Surveillance, Office of Surveillance and Biometrics, CDRH, and a June 24, 2004, presentation by Rosalie Bright, Epidemiologist, Division of Postmarket Surveillance, Office of Surveillance and Biometrics, CDRH (see, Gross 2004; Bright, 2004).

BOX 4.1
Excerpts from Examples of Reports Involving Children in FDA Adverse Event Database[a]

Device: Circumcision clamp
FDA Device Classification: Clamp, circumcision
Problem Description

Circumcision using [circumcision] clamp. Clamp was loose, resulting in laceration of the glans penis with loss of tip. Infant was transferred to another hosp for urologic consultation and surgery to repair damaged penis. (MAUDE Report No. 257649)

Device: Vacuum extractor
FDA Device Classification: Extractor, vacuum, fetal
Problem Description

Infant boy was delivered at [time] on [date]. Delivery was complicated by a prolonged second stage. Infant suffered hemorrhage beneath scalp at birth. Infant was admitted to neonatal intensive care unit and was placed on ventilator at [time]. Infant expired at [time] on [date]. The cause of death was the hemorrhage. It is speculated that the hemorrhage resulted from the use of a vacuum extractor with a defective gauge. Gauge on the device registered in the green "safe" zone even though excess vacuum was being produced. This defect was confirmed by testing the device using a pressure transducer. There would have been no way the user of the device would have known that the gauge was defective and that a dangerous level of vacuum was being produced . . . Device manufacture date is 1/17/96. (MDR Access No. M763107)

Device: Nasal dressing
FDA Device Classification: Bandage, liquid
Problem Description

The nasal dressing was placed in the pt in 2004 subsequent to sinus surgery. Two days later the nasal dressing fell apart while trying to remove it. The hosp health professional tried to remove the dressing again in 2004 and was unable to do so. The next day the dressing was surgically removed.

Manufacturer Response

User was not able to provide lot number, therefore mfg data is unavailable. The device did not fail, but was apparently cut or teased apart in an attempt to remove it. Surgically removed sample showed the pvc pouch with foam inside was fully intact, three weeks following initial surgery; indicating that the core of the product did not come apart; but was wedged and had to be surgically removed. User selected a 3 cm adult size contributing to the difficulty of removal. More suitable choices, when dealing with a small child's anatomy, include: the smaller removable dressing; model rr 200 which is 1/3 smaller than the device used. The dissolvable dressing; commonly used for pediatric cases because they can be trimmed to fit any size/shape anatomy, and do not require physical removal. (They dissolve away over time.) (MAUDE Report No. 1064611-2004-00002)

Device: Reusable I.C. nebulizer with tubing
FDA Device Classification: Nebulizer (direct patient interface)
Problem Description

Reporter feels 2 safety issues re: device are not being addressed by mfr. 1. Mouth piece has 8 mm × 17–18 mm rubber flap that disconnects easily. Reporter has found a child with this in its hand. 2. Same flexible rubber used for inside screw cap. Size is 12 cm which could easily be pulled off and block child's airway. Response from mfr was that user should read instructions. Many of the users cannot or will not read instructions completely. This device is mainly for home use. (MAUDE Report No. 492408)

Device: Pediatric peritoneal dialysis system
FDA Device Classification: System, peritoneal, automatic delivery
Problem Description

Home patient's (hp) foster mother reports a system error 2240 alarm in a drain during treatment on the homechoice machine. At the time of the alarm hp's foster mother noticed the homechoice set pt line had disconnected from the hp's transfer set. Hp's healthcare professional (hcp) and foster mom both state that foster mom was not properly connecting hp's transfer set to the homechoice set pt line and this is what caused them to disconnect. Hcp administered prophylactic antibiotics. Hp was admitted to the hospital on 12/14/99 for diarrhea and at the same time was monitored and subsequently diagnosed with peritonitis. Hp was discharged from the hospital on 12/21/99. Hp's course of treatment is vancomycin 25 mg/l for 10 days and gentamycin 10 mg/l for 10 days.

Manufacturer Response

Hp's foster mom just started taking care of this child about one week prior to this event and states she had no training on how to connect his transfer set to the homechoice set pt line. Since this occurrence the foster mom has received training from the hcp on sterile technique, operation of the machine and how to connect hp's transfer set to the pt line. (MAUDE Report No. 1423500-1999-01553)

Device: Infant heel warmer
FDA Device Classification: Pack, hot or cold, disposable
Problem Description

In preparation of capillary blood draw, a liquid infant heel warmer was applied to pt's foot causing a 2nd degree burn covering 33 percent of the foot.

Manufacturer Response

The suspect device was discarded by user facility. Lot info is not available. Health care provider could not verify that packet was "kneaded" for 30 to 60 seconds as indicated in instructions for use. Heel warmer was secured to pt by 2 "pampers." There is no indication in the instructions for use to do this, however there is no contra indication either. (MAUDE Report No. 1216677-2004-00012)

(continued on next page)

BOX 4.1 Continued

Device: Several
FDA Device Classification: Catheter (gastric, colonic, etc.), irrigation and aspiration
Problem Description

[This company] does not manufacture device #3. A copy of the report has been forwarded to that company. The iark-2 used in this case was from a lot #081001. It was manufactured by the previous ma location, and was not sold to the reporting facility. The device was disposed. No evaluation of the actual device is possible. The autopsy report is not yet available. It cannot be reliably determined if the device contributed to the death as no allegations or data exist of the device malfunctioning. Bowel perforation is a consequence of this procedure that is fully documented in the literature and instructions for use. No other incidences have been reported to date. Company will continue to monitor and investigate this incident as info becomes available. The catheter/tip used in these procedures is determined by the radiologist based on the size of the pt. Company is aware of other institutions using Foley type catheters for smaller infants. The pt prior to the procedure had a 3 day history of symptoms and complaints before presenting to the reporting facility. (MAUDE Report No. 1222612-2004-00001)

[a]Manufacturer name, report dates, and other details not included here. Abbreviations and other grammatical usage retained as in the original except for correction of simple spelling and similar errors.
SOURCE: FDA Manufacturer and User Facility Device Experience Database (MAUDE).

electrical failure, balloon rupture) (see FDA, 2001a,b). These outcome codes help agency staff to set priorities for the review of reports.

The first priority for FDA analysts is the review of reports of "Code Blue" events, the list of which includes pediatric deaths, multiple deaths, fires, explosions, or anaphylactic reactions. The contractor who first receives and codes adverse event reports notifies staff of the Center for Devices and Radiological Health (CDRH) within 24 hours of receiving a report of one of these events. Certain events—such as a cluster of injuries in a single facility—may prompt an emergency response. Otherwise, an investigation may lead to a public health notification, change in labeling, or other response based on the conclusion that a problem exists with a device or its use. An investigation may also lead to a determination that no action is warranted because the event was not related to a problem with a medical device or its use. The CDRH analysts who review reports are, in general, responsible for groups of products that are associated with a medical specialty or that have common design or material characteristics.

Less than 1 percent of reports involve high-profile events. In fiscal year 2003, the major problems identified through analysis of adverse events

included failures in aortic connector devices that resulted in hemorrhage and death, meningitis associated with cochlear implants, aneurysm-related deaths associated with endovascular grafts, hospital bed fires, toxic shock syndrome associated with a particular brand of tampon, off-label use of an adhesion barrier, and saline leakage in the access port of the lap band adjustable gastric band (FDA, 2004b). Some of these problems were identified through relatively short-term analyses of a few event reports, whereas others were the result of a retrospective analysis of up to 10 years of reports. Responses included FDA public health notifications or manufacturer withdrawals of products.

"International vigilance reports" are also a high priority for staff review. These reports are transmitted by agencies ("national competent authorities") responsible for surveillance in other countries. They typically involve the recall of products that have significant potential for harm.

The next priority for review is reports of events that are not in the high-priority category but that are also not so familiar that they are either reported through the summary report option described in Chapter 3 or identified by an automated report screening process (see below). These intermediate-priority reports account for about a third of the total. Again, reviewers may determine that no follow-up action is needed or they may recommend follow up.

The lowest priority for review applies to summary reports and reports flagged by an automated screening process that searches for certain well-recognized device-event combinations (e.g., silicone breast implants and capsular contracture, which is a tightening of the scar tissue surrounding an implant). Summary reports now account for about half of all reported events. The automated screening procedure picks up or flags about 15 percent of individual reports, and about 10 percent of these reports are reviewed by staff each month but only as a check that the screening tool is performing as intended.

Although FDA staff generally do not look for trends or changes in the summary reports and the reports flagged by the automated screening process, manufacturers (under the quality systems regulations described in Chapter 3) are supposed to monitor their event reports for trends and changes in frequency or severity of adverse events. Such monitoring could prompt further investigation and action (e.g., a recall).

Except for the small group of high-profile events, no specific rules define when a single report or series of reports should prompt further investigation of MAUDE reports, follow-up inquiries to manufacturers or facilities, epidemiologic study, or review of the clinical literature. Reviews and assessments of reports and other information about device hazards and judgments about appropriate FDA responses have a considerable subjective component. Resource constraints limit the agency's ability to

investigate reports that do not involve deaths and other high-profile events.

It is worth reiterating that in addition to adverse event reports, FDA may learn of potential problems with a marketed device or its use in other ways, including during inspections of facilities and as part of ongoing manufacturer efforts to refine and improve a product. Problems may also be detected during postmarket clinical studies sponsored by manufacturers, the National Institutes of Health (NIH), or others. Other avenues of problem identification include published case reports of unusual or unexpected problems, presentations at medical conferences, or informal conversations associated with such meetings. Such conversations were an early indicator of a possible link between cases of meningitis and cochlear implants (see Appendix F).

ANATOMY OF ADVERSE DEVICE EVENTS: ILLUSTRATIVE VIGNETTES

"I never really thought about reporting that [problem] in particular. . . . There are just millions and millions of things that can go wrong."

Melisande Statz-Hill, parent, 2004

This mother of a young child cared for at home with multiple medical devices was making two points. First, it did not occur to her to report (even to the home health agency) a problem that seemed to involve error in the use of a device—in this case overtightening by a nurse of ties for a tracheostomy tube—rather than a malfunction of the device itself. The second point was that the opportunities for something to go wrong—even for a family with private-duty nursing support and a home health company that specialized in pediatric patients—seemed endless.

To illustrate the many kinds of adverse device events (and device malfunctions and close calls) and the challenges of analyzing such events, the committee developed several vignettes or synthetic case histories. They are intended to convey both the diversity of device events and the interplay of variables associated with events and their aftermath. These variables include the complexity of the device and its management, the setting of care and its characteristics, the characteristics of the patient (e.g., developmental stage), the circumstances of the family (e.g., understanding of how to operate a device correctly at home), the opportunities for (or impediments to) reporting the event, and the resources brought to bear on understanding the event. The examples do not attempt to represent proportionately the distribution of reported (much less actual) adverse events by type of device, problem, or reported consequences.

Each story below is simplified to highlight issues of interest. Some describe situations that are reasonably common and even accepted as "nor-

mal" (albeit unwanted). Others describe unusual situations that especially challenge those attempting to understand the event and prevent it from occurring again. Most of the stories point to the importance of considering human factors (human behavior and human systems and their interaction with devices) in the design of devices and the interconnection of devices and their accessories.

Although this report has tended to focus on more complex, high-risk medical devices (mainly Class III devices) that undergo clinical testing, several of the vignettes underscore that serious adverse events often involve less complex but very widely used devices such as catheters, accessory tubing, and syringes. Other vignettes describe problems associated with long-term use of an implanted or partly implanted device, that is, problems that cannot be expected to be evident in the relatively short-term clinical studies that are usually submitted as part of the FDA approval or clearance process for medical devices. Absent systematic long-term studies of medical device safety and effectiveness, such adverse events—as well as rare short-term events—may only slowly reveal themselves in usual clinical care. The importance of long-term studies of medical devices used with children is discussed further in Chapter 6.

Each vignette is synthesized from a variety of sources, including case reports in the medical literature, reports in FDA's adverse event database (MAUDE), training materials for the MedSun program, experiences of committee members, presentations or discussions during public committee meetings, webpages for clinicians and patients and their families, news reports, and similar sources. No example depicts specific child and family circumstances exactly, although each story draws from real experiences. The fictional names, personal situations, and institutional details have been created to add a human dimension to the abstraction of adverse event or case reports and also to underscore points emphasized in this report.

Vignette A: Close call with aspirated syringe cap. *This vignette involves a close call with a simple medical device, a syringe with a cap. Other children who have aspirated syringe caps have died. The example highlights the importance of careful communication with parents about the safe use of simple but potentially dangerous devices.*

The father of 9-month-old Julia brought her to the primary care clinic because she was clearly uncomfortable and seemed to be running a fever. The doctor diagnosed an infection and prescribed an oral antibiotic to be administered with a syringe. He gave Julia's father illustrated instructions and also demonstrated

how to use the syringe, which was not an oral syringe for medications but a needleless hypodermic syringe with a fenestrated cap that allowed medicine to be drawn into the syringe with the cap in place.

That afternoon Julia's father drew the medicine from the bottle through the fenestrated cap into the syringe, but he stopped to answer the phone. When he returned, he administered the medicine by placing the tip of the syringe into the child's mouth, not noticing that the clear cap remained on the syringe. The baby immediately started gagging, and the father realized he had forgotten to remove the syringe cap. He quickly placed the child on his shoulder as he called his wife; a few seconds later he saw the cap in his daughter's mouth and retrieved it. Although she was screaming, she was no longer gagging or gasping.

Julia's parents raced her to the clinic, where a doctor evaluated the child, finding her upset but okay. After calming Julia and her parents, this doctor substituted an oral syringe—with a very distinctive cap—for the parents to use for measuring and administering the antibiotics.

Consistent with the clinic's patient safety and quality improvement policies, the doctor reported the problem internally. The clinic patient safety officer found other reports in the medical literature of aspirated hypodermic syringe caps, some involving deaths. By the end of the year, the clinic had put in place a policy that only oral syringes should be used in the delivery of oral medicines with infants and small children, and staff were working on better education strategies for parents, including a "teach back" step during which the patient or caregiver demonstrates use of the device to the physician or nurse. The safety officer reported the event to FDA, even though it was not required. Nonetheless, the "lessons learned" were essentially confined to the clinic.

Device involved: Hypodermic syringe.

Proximate cause: Lay user error.

Institutional/system factors: Communication shortfall—use of device demonstrated to parent but without "teach back" or "show me" step to assess the parent's understanding; lack of warning about the cap hazard; clinic or physician choice of (less expensive) hypodermic rather than oral syringe that is designed for administration of liquid medications by mouth; failure of physician/health care team to remove cap of hypodermic syringe prior to giving it to parents to use.

Design factors: Presence of cap obvious when syringe used for injection, but hazard less apparent with oral use; fenestrated cap design allowed cap to stay in place while medicine was drawn into syringe.
Comment: Safety principles would suggest removing the opportunity for human error altogether, that is, redesigning the device because there will always be the potential for user (especially a lay user) to forget instructions or fail to appreciate risks and dangers.
Further reading: Kurtzweil (1994); *Family Practice News* (2000); ISMP (2001); Schillinger (2004).

Vignette B: Circumcision clamp injury. *As described later in this chapter, injuries involving circumcision clamps have prompted an FDA safety alert. In this story, hospital personnel were unaware of the alert. As in this incident, inexperienced users of a device—even a "low-tech" circumcision clamp—contribute to adverse device events, but deficient hospital systems of training and credentialing for procedures—which would likely not be mentioned in an adverse event report—can play a role.*

The physician, a new pediatric resident, was preparing to circumcise newborn baby John. The basic instrument was a Mogen-type clamp. The resident had watched the procedure several times and had been supervised while performing a few. During the procedure, the baby suffered a slight laceration of the penis. Fortunately, the injury was minor and easily treated, but the baby was kept an extra day in the hospital. More serious injuries—including amputation—have been associated with clamp defects and procedural errors.

The hospital investigation revealed that the physician had limited experience in performing the procedure and lacked training with the device model used, its assembly, and the safety measures specific to that device, including inspecting the clamp for size and alignment. Investigators found that components of the device were not properly aligned, and the device had been incorrectly repaired using incompatible replacement parts. They could not determine when the device had last been inspected for alignment. FDA and other warnings about problems with certain circumcision clamps were unknown to physicians within the hospital. The hospital considered the injury to be too minor to require a report to the manufacturer or FDA, but it did institute a new policy for routine inspection of clamps.

Device involved: Circumcision clamp.
Proximate cause: Use error: physician failed to determine that the device used met use specifications and was undamaged. An experienced user, or one adequately trained with the use and assembly of the device used, might have recognized a problem before harm occurred.
Institutional/system factors: Inadequate training; inadequate procedures for disseminating manufacturer and FDA advisories and making appropriate changes in internal policies and practices; incorrect repair by hospital personnel; lack of policy to label clamps to indicate size; lack of policy for periodic inspection of device for wear or proper alignment.
Design factors: Design prone to misalignment.
Comment: The process of physician education and training is changing from the traditional "see-one, do-one, teach-one" approach to "see several, ask questions (e.g., about differences in patient anatomy and clinical situations, what risks to anticipate and prepare for) and then do several procedures under direct supervision to evaluate procedural and evaluative skills and judgment before eventual independence."
Further reading: ECRI (1999); FDA (2000g).

Vignette C: Deprogramming of cochlear implant. *Children's play can affect device performance. In this case, the static electricity charges generated by playground equipment created enough energy to deprogram a cochlear implant, requiring surgical replacement. Prompt reporting and evaluation of such events can lead to device modifications that protect future children.*

Some years ago, during an afternoon visit to the home of her cousins, Jennifer went with the rest of the family to a nearby park, where the cousins enjoyed using the playground equipment. Jennifer had been born with severe hearing loss. When she was 18 months old, she received a cochlear implant. With intensive language development therapy, she did very well.

After returning from the visit, Jennifer complained that she couldn't hear. A few days later, after he had extensively questioned Jennifer and her mother, examined the implant site, and performed a diagnostic assessment of the device, the surgeon who had implanted the device confirmed that it had failed. Based on some past

experiences and conversations with colleagues at conferences, he suspected that device had been damaged by static electricity from plastic playground equipment. He scheduled Jennifer for surgery to remove the device and implant a newer model. He also told Jennifer's mother what he thought had happened and reassured her that it was nothing she could have been expected to foresee.

The surgeon sent the explanted device to the manufacturer with a description of the circumstances and his conclusions. Such reports led to refinements in the device materials and electronics to shield the implant's circuits from damage and protect the software programming from being changed by static electricity charges. The manufacturer changed the implant's labeling to caution physicians, families, and, when appropriate, patients about the wide variety of activities that may lead to a static discharge.

Device involved: Cochlear implant.

Proximate cause: Exposure of device to electrostatic charge.

Institutional/system factors: Possible underreporting and slow investigation of risks to device performance based on problem reports.

Design factors: Lack of shielding and filtering to protect against static electricity.

Comment: The device's design did not anticipate certain environmental hazards, for example, the build-up of an electrostatic charge as a child uses a plastic playground slide or a tubular slide in an indoor play center. Even getting into a car with new tires can result in electrostatic energy when a child touches the door handle. Reports of implant deprogramming have led to design refinements, including changes in materials (e.g., plastic replacing metal in the external processor unit), which allowed for better isolation of static electrical energy. In addition, devices can now be reprogrammed by an external computer (taking less than 5 minutes), for the occasion when a child finds that plastic slide irresistible.

Vignette D: Orthodontic headgear injury. *In this vignette, a child's orthodontic headgear became dislodged while he was sleeping, and one of its sharp and pointed metal arms embedded itself in the child's lower eyelid. Orthodontic headgear is commonly prescribed by orthodontists to correct the alignment and position of the teeth. Safe use of devices by patients or families depends on their adequate education and understanding of safety issues, including how*

to handle a very sharp and pointed object when applying it, removing it, or otherwise living with it.

Twelve-year-old William was very fortunate. He was wearing orthodontic headgear—sometimes called a facebow—that had been prescribed three months earlier to straighten his misaligned teeth. One morning he awoke with a sharp pain under his eye. His cry of pain brought his parents to his room, where they found a laceration just below their son's right eye. The ridged, rod-like arm of the headgear had somehow become dislodged, and its sharp tip had sprung out to cut the boy's face. His parents called the orthodontist, who recommended that they go to the emergency room; instead, the parents took the boy to his pediatrician who examined him and stitched the laceration. After consulting with the pediatrician, William's mother took him to another orthodontist, who determined that a safer device would be suitable.

No one involved understood that the incident could be reported to FDA or thought about reporting it to the manufacturer. The boy's former orthodontist was relieved not to be involved in a lawsuit. He did not reconsider his practices for using facebows, perhaps because he thought that might indicate that his practice had been deficient.

Devices involved: Orthodontic facebow.

Proximate cause: Device design, including hazardous points, allowed dislodgement from user movement during sleep.

Institutional/systemic factors: Poor communication about a hazard with rare but sometimes severe consequences; continued professional use of hazardous device design despite subsequent development and marketing of safer devices for most situations.

Design factors: Importance of taking use environment (motion during sleep) into account; safer designs available for many patient situations.

Comment: Fear of litigation may be a disincentive to reporting or acknowledging problems. Professionals who are primarily involved in office-based care may not be aware of reporting options or may find reporting burdensome.

Further reading: Samuels and Jones (1994); Samuels et al. (1996); Blum-Hareuveni et al. (2004); WTTG (2004).

Vignette E: Infection from flawed bronchoscopes. *Infections have many possible causes, and linking a device to an infection can take*

time. In this case, good hospital infection control systems led to a fairly early identification of a problem that led to recall of a medical device. Not all hospitals were successfully notified of the recall.

Jerry was a 2-year-old who thought his mother's shiny round earrings looked good enough to eat—so he tried. He choked, and the earring went directly into his windpipe. His parents took him to the emergency room of a nearby hospital, where an X ray showed the earring was lodged about 5 inches below his vocal cords. To retrieve the earring, the doctor used a bronchoscope, a tool that allows the physician to see the inside of the airways, remove foreign objects, take samples of tissues or secretions, or clean out obstructed or infected areas.

After an otherwise successful procedure, Jerry developed a bacterial infection that is common in patients with cystic fibrosis but uncommon in patients with normal lungs like Jerry. The bacterium was quickly identified and successfully treated with a short extension of Jerry's hospital stay.

Shortly afterward, hospital infection control and epidemiology staff identified an increased incidence of this kind of infection in patients not normally at risk. Their investigation identified the bronchoscopy procedure as a common factor among affected patients. This focused their attention on the facility's bronchoscopes and the procedures for cleaning, disinfecting, and inspecting them between uses. After intensive scrutiny of the devices and the procedures, they suspected that the design of one of the devices played a role.

In the meantime, through their professional contacts, the infection control staff learned that similar problems had recently been reported to the device manufacturer and FDA. Several weeks later, through the same informal communication channel, they learned that the manufacturer was recalling the device, and several days later, the risk management department received a letter to that effect. All involved were surprised to see subsequent news stories about problems at a prominent academic medical center whose physicians had not been promptly notified of the bronchoscope problem and recall because the notification letter had been misdirected. Although the risk management staff would still use their professional network, the department decided to subscribe to an online device recall tracking system to provide an extra margin of security against delayed or misdirected recall notifications.

Devices involved: Bronchoscope; bronchoscope reprocessing units.

Institutional/systemic factors: Lack of effective and timely procedures for problem notifications and recalls to facilities and professionals.
Design factors: Design of a threaded bronchoscope port connector that could not be adequately cleaned or disinfected.
Comment: Devices may not be initially suspected as sources of infection, and making a definitive link can involve considerable investigation and testing. Manufacturers and hospitals have room for improvement in managing device recalls.
Further reading: FDA (2002k); Jurasek (2003); Kirschke et al. (2003); Srinivasan et al. (2003, 2004).

Vignette F: Effect of growth on implanted defibrillator. *Implants and other devices used with adults are often adapted for use with children by simply making the devices smaller. For implants, the use of a smaller device may be adequate initially, but the child's growth may eventually require replacement with a larger implant. For some devices, this is expected, but for others, growth-related issues only become evident through long-term follow-up. This vignette describes the latter situation.*

Maxine was 3 years old when she was diagnosed with Long Q-T Syndrome, a rare condition that episodically and unexpectedly caused her heart to beat so fast that it would not pump blood effectively to her brain and other vital areas. She required electrical shocks to save her life. After several drugs to control her heart's electrical activity proved ineffective, the child's cardiologist suggested a surgically implanted cardiac defibrillator (ICD) that would monitor the heart's rhythm through wires (leads) placed on the sensitive areas of electrical activity within the heart. If the device detected an unsafe rhythm, it would fire a shock to Maxine's heart. ICDs have saved the lives of many adults and children.

The device fired twice during the next 4 months, each time averting a full cardiac arrest. Maxine's parents continued to take her to the cardiologist every 4 months for follow-up studies of the device's functioning. They got good reports during each of these visits.

Then one morning, Maxine suddenly fell to the carpet, clutching her chest and crying. As he was trained to do, the father immediately called 911. At the hospital, doctors determined that the device had misfired and had given the girl a shock. Based on a chest

X ray, hospital staff concluded that one of the leads had fractured. Possibly it had been stretched during a growth spurt following the child's most recent visit to her cardiologist. Maxine's parents were surprised to learn that nontherapeutic firing of shocks was a known problem. Physicians said that ongoing monitoring of the device was the best way to check for lead fractures or changes in lead position, but periods of rapid growth could sometimes cause the kind of problem Maxine experienced.
Devices involved: ICD and leads.
Proximate cause of adverse event: Device malfunction, unintended shocks.
Institutional/system factors: Limited counseling of family about potential for device performance problems and, hence, the need for lead monitoring and replacement as the child grows.
Design problem: Possible lead failure due to patient growth; device not returned to manufacturer for analysis.
Other comment: The ICD has been studied intensively with adults, but pediatric studies are scattered. Large groups of pediatric patients have not been studied prospectively. One study of 29 patients found 38 chronic complications, the most frequent being lead failure. Interestingly, the size of child at the time of the implant was not a factor in outcome, but *growth* of the child in weight, height, or surface area was directly correlated with lead failure. Unfortunately, researchers have not identified a clear threshold for predicting such failure and have called for a large prospective study, perhaps using a multi-center registry or network.
Further reading: Silka et al. (1993); Alexander et al. (2004).

Vignette G: Fatal data entry error. *For operators of medical devices, understanding of and adherence to safe procedures for entering and checking patient and treatment data for medical devices is critical. Familiarity with the routines of data entry can lead operators to take shortcuts, forego cross-checking or rechecking of information, and assume incorrectly that a device is operating consistent with the treatment plan. In this vignette, data entry errors and failures to check dose levels led to the administration of lethal levels of radiation.*

Billy had been diagnosed with brain cancer at age 10. His long-term prognosis was not good, but his physicians thought radiation

treatment could provide some additional years of reasonably good quality life with his family. At the very outset of the treatment, a hospital staff member incorrectly entered the radiation dose information, and no one ever again confirmed the prescribed dose with the settings on the radiation therapy unit. Four weeks after the final treatment, Billy experienced progressive skin eruptions at the area where the radiation beam was directed. A consulting dermatologist questioned the medical physicists at the treating facility about the radiation treatments. The boy's physicians concluded that he had been exposed to a severe radiation overdose. A few months later, Billy died.

Once attention had focused on the radiation dose, the hospital called in a consulting engineer to investigate. When he checked the settings in the electronic memory of the therapy unit, he discovered the dosage error. The facility's staff began to fault the equipment's software for not catching the error, but the engineer inquired whether the erroneous setting was a correct setting for any category of pediatric patient. It was. The system's software would have not "queried" the dose for that reason. At the time, the institution did not have real-time dosimeters that would have detected the dose error. The hospital settled a lawsuit brought by Billy's parents.

Devices involved: Linear accelerator, radiation therapy simulator.
Proximate cause: Staff error in entering data and failure to check the treatment settings against the prescribed dosage before each treatment.
Institutional/system factors: Failure to follow institutional policy to double check data entry before each treatment; lack of real-time dosimeters; inappropriate staff reliance on software to detect error (dose was not outside the range for all patients); inadequate staffing of radiation oncology department.
Device factors: Poor software design of data entry menu.
Further reading: Adapted from FDA (2002n, Case Study 16). For a report on serious radiation device adverse event involving software, see Doyle (2000).

Vignette H: Growth-related complication from gastrostomy tube (g-tube) design. *A device designed for use with adults may not be suitable for a growing child. In this story, the doctors chose a*

specific gastrostomy tube because it could be placed with less invasive surgery and the design featured a disc that provided just enough tension to reduce leakage. As the child grew, the disc-tension design caused too much pressure, which caused the disc to embed in and then erode through the stomach wall.

Robert, now 14, had survived a serious brain injury when he was 12. His parents visited him daily at the rehabilitation hospital where he received physical therapy and supportive care. The family was grateful for his gastrostomy tube, which allowed him to receive all of his nutrition through the tube inserted directly into his stomach. This tube had been placed 17 months ago in the radiology suite of the adult hospital where he was originally treated. It had seemed to work well, but then the area adjacent to the tube showed leakage and some redness.

The rehabilitation hospital decided it was prudent to return Robert to the original hospital for evaluation. The work-up there found that the inner disc of the tube, which held it against the stomach wall, had actually burrowed into the inner lining of the stomach, going completely through the stomach wall. Surgeons had to remove that portion of the stomach where the disc was buried. They placed a different type of gastrostomy tube during the surgery, which required an additional 2 weeks of hospitalization. When the parents learned that the new gastrostomy tube would not cause the same problem, they asked why they were not told of the risk with the original device and whether the problem had been reported. They wanted other parents to be vigilant about this complication if it was possible.

Devices involved: Percutaneous gastrostomy tube with triangular retention disc.

Proximate cause: Tension from fixed distance between internal and external discs of the g-tube, which caused pressure on the tissues of the child's growing abdominal wall; embedding of corners of triangular-shaped internal retention disc not noticed, possibly due to the child's inability to communicate discomfort in a specific manner.

Institutional/system factors: Lack of procedures to evaluate distress in patient with communication limitations; lack of adequate protocol for monitoring implanted devices in such patients; tube placed by radiologist who would not be expected to be involved in follow-up management of the device; no apparent hand-off of device management to other physician involved in child's care.

Design factors: Lack of device mechanism to measure the disc tension or allow adjustment for a child's growth; failure of device labeling to mention growth considerations; disc shape possibly contributed to embedding.
Other comment: Authors of a case report on this problem recommend checking the tension of the device by regularly spinning the tube around the retention disc. They also suggest scheduled replacement of the tube, given the predictable growth of a child's abdominal wall. Some pediatric gastroenterologists favor tubes with circular retention discs but would still recommend replacement of these with a device that did not provide such tension as soon as the ostomy track was mature. In children's hospitals, placement by interventional radiologist is probably not standard practice (personal communication, Norberto Rodriguez-Baez, M.D., Division of Gastroenterology and Nutrition, Department of Pediatrics, University of Texas Southwestern Medical Center, March 24, 2005).
Further reading: Cahill et al. (2004).

Vignette I: Parent's mistake with home infusion pump. *As in this story, treatments once confined to hospitals are also taking place in the home and school. Parents and others now provide care and cope with medical devices—and problems—that formerly were the domain of health professionals. Training for parents on how to operate a device may be limited and include neither directions on how to assess or troubleshoot problems nor evaluation of a caregiver's capacity to deal with mistakes or malfunctions.*

Katie was 2 years old when she was diagnosed with a resistant bacterial infection of her femur. She was sent home with an infusion pump that would deliver several weeks of intravenous (IV) antibiotics through a central venous catheter. While in the hospital, Katie had gone through four different standard IV lines (catheters). Few usable vein sites were left, so she received the central line. Katie's mother attended classes at the hospital on how to manage the line and change the dressings around the skin entry site. She was confident that she had the necessary skills and information to participate safely in her child's care. A nurse was to come out to the house for at least one of the three doses per day.

One evening, Katie's mom was feeling particularly frazzled and distracted because both siblings were fussing and her husband was

out of town. She forgot to prime the tubing—that is, fill it with fluid to remove air—before putting the tubing into the cassette unit of the automatic pump and then attaching that set-up to her child's IV. After she turned the pump on, it sounded an alarm within seconds, and the pump display clearly read "air in line."

Katie's mom turned off the pump, removed the tubing from the pump's cassette, and desperately tried to remember what to do. Meanwhile, the air in the IV line migrated through the tubing into Katie's veins. The child stopped breathing. As she had been trained to do, Katie's mom gave her rescue breaths, which revived the child. The mother then saw that she had not clamped the tubing with the air in it and immediately realized what had happened. She called 911 and an ambulance took Katie to the emergency room, where she was treated and released. Subsequently, Katie's mom took the girl to the hospital's emergency room for all of her antibiotic doses until the infection resolved.

Devices involved: Portable IV infusion pump.
Proximate cause: Failure to prime tubing (remove air from tubing) prior to connecting tubing to patient's IV; failure to clamp tubing.
Institutional/system factors: Inadequate parent education on safe device operation and troubleshooting; possible poor selection of patient for family-delivered home therapy (multiple children, only one adult routinely at home).
Device factors: Lack of warning messages other than "air in line" on the device display; no message to "disconnect tubing from child" or "clamp tubing close to the child."
Further reading: Laskey et al. (2002).

Vignette J: Injury from pediatric use of orthopedic device. *This story illustrates how adverse outcomes can occur when physicians lack sufficient information to guide the use of complex, high-risk devices with children. In this example, a child with severe facial abnormalities underwent craniofacial reconstruction using a complex rigid external distraction osteogenesis device.*

Howard was born with his upper jaw and cheek area so underdeveloped that his lower jaw protruded and his teeth were misaligned. His eyes looked like they were sinking into his cheeks, and his underdeveloped midface and crowded airway created speech problems. When Howard was almost 8 years old, his parents con-

sulted a craniofacial group that offered "stretching" of the child's midface using a process similar to that used earlier to widen his palate. The process, which is common in orthodontal work, is called distraction osteogenesis. It takes advantage of the fact that bones are constantly remodeling, especially in the growing child or in healing bone. During the procedure, the surgeon strategically makes cuts in the bone, after which traction is applied to maintain a specified distance between the bone segments. Active bone-building cells then construct new bone to fill in the gap and thus elongate the bone. The procedure had been well studied in the elongation of leg bones in adults, but now the surgeons were applying the theory to the complex set of bones of a child's skull and face.

During surgery, the base of the device system, called a halo, was screwed into Howard's skull to anchor various rods, bars, and brackets attached to his facial bones. Shortly after Howard's discharge from the hospital, the area around two of the screws in his skull had become very red and swollen and was draining yellowish material. A CT scan showed that the screws had gone too far into the skull and were touching the brain's surface. Surgeons removed and replaced the screws, but after two more days, doctors found the new screws had actually gone partially into the brain. Fortunately, Howard suffered no brain damage. No one could explain how the problem happened; the boy had only been lying in bed or on the couch at home.

After removing the old hardware, doctors tried a new device still under testing and development. This device allowed for more facial and mouth movement and also for more precision in setting the force and angle of force that the tension bars applied to the halo element that is attached to the skull. This device worked well and within 2 years, Howard had good functional and cosmetic results. Still, his parents wondered about how the child's growing bones would develop because the device was too new to have long-term results. Howard's physicians read about a very similar case in a journal case report, which mentioned studies of the halo device but noted the lack of data about important questions in pediatric use of the device.

Device involved: Modified halo rigid external distraction system.
Proximate cause: Excess force applied to skull bones by traction apparatus; direction of force and lesser thickness and density of child's skull also likely factors.

Institutional/system factors: Lack of agreed-upon guidelines for the use of procedures that have not been evaluated with children; lack of commitment to systematic long-term evaluation of complex orthopedic devices.
Design factors: Manufacturers and clinical investigators have not systematically studied or modeled the complex force vectors required in the application of this type of device to developing bones in a child's face and skull.
Other comment: Absent systematic clinical studies, physicians using complex devices may lack adequate instructions about safe and effective methods of application and appropriate patient follow-up and monitoring. They likewise may lack sufficient information about the prospect of long-term benefits and short-term and long-term harms to guide clinical and family decisions about the use of a device with children.
Further reading: Dormans et al. (1995); Le et al. (2001).

Vignette K: Difficult-to-detect implant problem. *This story provides another example of how an ill child's physical dimensions can affect device performance. With attentive parents who consulted and followed the device manufacturer's instructions, the child received the careful evaluation needed to reveal a difficult-to-detect problem. Delay could have been fatal; catheter malfunctions with this device have been linked to deaths of both children and adults.*

The parents of 4-year-old Sarah found themselves confused by their daughter's increasing muscle tightness, high fever, and itching. Sarah had cerebral palsy, but they had not seen her muscles twisted up like this since she'd had an intrathecal Baclofen pump placed in her abdomen. The hockey puck-sized pump delivered the muscle-relaxing Baclofen drug through a small catheter to the spinal fluid. Before that, Sarah's muscle spasticity meant that she could not walk easily or play like other children.

Then the pattern changed, and Sarah showed signs of lethargy; her muscles seemed too "floppy" rather than too tight. To her parents, she seemed to have switched from showing symptoms of an underdose to showing symptoms of an overdose, at least according to the information on a wallet-sized card supplied by the pump manufacturer. The card, which Sarah's parents consulted as had been stressed by the child's physicians, instructed patients to

check immediately with their neurologist. The neurologist found that the pump's battery and reservoir of medication were adequate but that the girl's symptoms were consistent with Baclofen withdrawal. He ordered a study to check, in particular, the integrity of the tubing. The study showed no leaks, but the doctor recommended a surgical evaluation, given that Sarah was getting more and more ill. Surgical exposure of the device revealed that the tubing was cracked in the segment closest to the pump, an area of the tubing that is relatively inflexible and that passed over the bony prominence of Sarah's pelvic bone. Like many children with cerebral palsy, Sarah was seriously underweight, so she had little padding to prevent tubing wear at the site it passed over her bones. The surgeons replaced the tubing.

Approximately 6 months later, Sarah again showed symptoms of an overdose. During another surgery, her doctors found the tubing cracked in the same area. (For technical reasons, it was virtually impossible to discover or verify this problem without surgical exploration.) This time, however, Sarah's neurologist and surgeon had read a report in a professional journal that concluded that the infusion pump needed to be placed differently in children such as Sarah, to avoid compression at a spot where the tubing was relatively inflexible. (The compression led first to an underdose and then to a fracture and subsequent overdose.) This seemed reasonable, so the surgeon adjusted his surgical procedure. He later learned that the manufacturer had adjusted its implantation directions.

Device involved: Intrathecal Baclofen pump.

Proximate cause: "Stiff" portion of catheter tubing in friction against active child's protuberant bone, causing "nick" or "crack" in tubing.

Institutional/system factors: Possible slow detection of problem due to underreporting.

Design factor: Device large relative to size of very young child with cerebral palsy (average 4-year-old girl with cerebral palsy weighs 24 pounds compared to normal weight of 35 pounds); stiff tubing stressed by initial implantation strategy.

Other comment: Extensive manufacturer website addressed many aspects of device operation and troubleshooting. The information and warnings on the manufacturer's information card helped parents to recognize problem and seek assessment that identified the life-threatening device malfunction.

Further reading: Coffey et al. (2002); Dickerman and Schneider (2002); Dickerman et al. (2003); Gooch et al. (2003).

Vignette L: Losing track of an implant. *This case illustrates a relatively "forgotten" device, one that was important during a child's early years but not in adolescence, when responsibility for device management shifted to the adolescent. This shift has risks as well as benefits related to adolescent inexperience and failure to appreciate or recognize the need for vigilance in device maintenance. Without ongoing involvement in device use or maintenance, parents may lose track of what is happening, especially if the device is not seen as critical to life and health.*

Elizabeth, a 16-year-old with cystic fibrosis, had a "port-o-cath" central venous catheter placed when she was 6 years old. This catheter had provided intravenous access for countless admissions and treatments for pneumonia, each requiring long courses of antibiotics. Once Elizabeth entered her teenage years, the surgically implanted device (which consisted of a self-sealing medication reservoir that was attached to a catheter that ended in the superior vena cava) was rarely used.

Elizabeth requested that she take over the device's weekly care, which involved flushing the catheter. The catheter was imbedded near her breasts and privacy had become paramount to Elizabeth. After following the routine successfully for an extended period, Elizabeth forgot to flush the catheter for several weeks. Then, when she tried it one morning, she had to exert great force and still was unsuccessful. Later that day at dance practice, she experienced sudden and sharp chest pain. The school called an ambulance, which took her to the emergency room of the hospital where she had been treated before.

When the girl's parents arrived at the emergency room, they told the staff that her lung disease was stable. Neither Elizabeth nor her parents thought to mention the central line, and the staff saw nothing in the girl's medical record that alerted them to the line's presence. (Mention of the device was buried in progress notes, and the record included no device equivalent of a medications list.) Because Elizabeth was having trouble breathing, the emergency personnel obtained a chest X ray, which showed that the catheter had separated from the reservoir and had migrated through the vein into the right side of the heart, with part of it headed out into the small vessels of the lungs. Elizabeth then told the physicians and her parents that the device had been neglected for some weeks and that she had been unable to successfully flush it that morning. She underwent surgery to remove the fractured catheter.

Device involved: "Port-o-cath" central venous catheter.
Proximate cause adverse event: Old central line tubing with thrombus formation that made it difficult to flush; likely fracture of line during forceful attempt to clear it.
Institutional/system factors: Lack of clear documentation in medical record at the hospital/emergency room citing device presence; incomplete medical history from patient and family; school personnel unaware of device and unable to advise emergency medical responders; patient's physicians lost track of device, failed to assess continued need for it, and failed to monitor patient adherence to and awareness of device maintenance requirements.
Design problem: Thrombus and fibrin clot formation common in catheters; lifespan of catheter system not known or publicized.
Other comment: Notwithstanding the importance of respecting an adolescent's developing maturity and the value of a wellness model of care, these patient-centered strategies risk a loss of vigilance with respect to device risks, safe maintenance, and adult oversight. The adolescent years challenge parents in many ways, especially when the adolescent has a serious but stable medical condition. In these situations, monitoring of a teen's health maintenance practices can be a source of tension, and teens may be reluctant to admit that they have not followed instructions and need assistance.
Further reading: Fratino et al. (2001).

Vignette M: Insufficiently evaluated procedure. *In this vignette, an interventional radiologist attempted to remove a clot from the end of a central venous catheter using a procedure that had been reported in the literature but not systematically evaluated. During the procedure, the tip of the original patient's central line sheared off and immediately drifted into the end of a vein within the lungs. The child suffered no immediate harm but required surgery to replace the catheter.*

After Hannah was diagnosed with acute lymphoblastic leukemia, doctors placed a central venous catheter in her chest to deliver the required chemotherapy. The catheter was used frequently for both delivery of medication (its primary purpose) and blood drawing for ongoing laboratory studies. For a 3-year-old facing six months of chemotherapy, easy access for blood draws reduced her pain and stress.

After 3 months, Hannah's catheter became clogged at the catheter tip. The catheter still allowed the free flow for chemotherapy but not for blood draws. The clog resulted from a natural process of fibrin formation that occurs on the end of every catheter that dwells within the lumen of a vein for an extended period. The interventional radiologist offered to perform a relatively new procedure that involved going into a vessel in Hannah's leg with a second catheter that had a loop at its end to grab and strip the fibrin debris off the end of the other catheter. The goal was to salvage the original catheter. This workaround had been reported in the pediatric interventional radiology literature and seemed reasonable given that the only alternative was to replace the catheter, a surgical procedure requiring general anesthesia.

During the procedure, the clot was stripped, but with it, the tip of the original central line sheared off and floated away, coming to rest deeply within the vessels of Hannah's lungs. It could not be retrieved. Hannah experienced no symptoms, but required another central line to be placed surgically.

The radiologist was completely surprised by the event, having never heard of or imagined such a possibility. She discussed the event with colleagues and reported it to hospital risk management, which did not evaluate whether it was reportable under FDA rules and did not otherwise investigate or act further.

Hannah's parents really did not understand what happened; they were focused entirely on their child's health and did not consider action against the hospital. The girl's oncology team wondered whether the expected benefit of trying the new procedure really justified the risk, which was not well defined because the procedure had not been systematically evaluated with children. The radiologist hoped to see future studies that assessed the risk of fracture or shearing of central venous lines when tension is applied to them during a stripping procedure.

Devices involved: Normal central venous catheter; modified central venous catheter.

Proximate cause: Use of device beyond its specifications.

Institutional factors: Lack of expertise and training in procedure; lack of opportunity for learning and early problem identification by others due to failure to report adverse event.

Design factor: Catheter prone to clotting.

Other comment: "Workarounds" (as described in Chapter 2) are common to fix or modify—rather than surgically remove and re-

place—a device that is implanted. This is justified if the risk incurred is low compared to replacement. When a procedure and the requisite skills have not been evaluated with significant numbers of patients, the risk can be difficult to assess.
Further reading: Knelson et al. (1995); Haskal et al. (1996); Bessound et al. (2003).

Vignette N: Fatal error in connecting tubing. *Correct assembly of devices is critical for safety. In this vignette, one tube was confused for another because their end-fittings looked similar. The result was fatal when a child's oxygen tubing, under pressure, was inadvertently connected to his IV pump. Although training nurses to assemble devices is important, a device design that would prohibit such a deadly hook-up would be more effective at avoiding this human error.*

Nurse Johnson independently cared for four children on a busy pediatric ward. One patient, 9-year-old Andrew, had been hospitalized after a severe asthma attack, requiring oxygen therapy and aerosolized treatments as well as IV antibiotics. He was absorbed in his video game when Johnson arrived to connect the tubing for his afternoon antibiotic dose. A respiratory therapist had just finished Andrew's breathing treatment, delivered using the oxygen source from the wall. She placed that oxygen tubing across the bed rail, but forgot to turn the oxygen flow off.

Johnson stepped in beside Andrew's bed and hung the bag and tubing of IV antibiotics she had carried in the room with her. Andrew complained that the nurse was in the way of his video game and she stepped aside. Then, when she reached over the video-game control wires, she mistakenly took hold of the oxygen tubing, the end of which was very similar to the tubing for the IV bag. She next fitted the wrong tubing to the pump, which was already connected to Andrew's IV in his arm. This sent air into the IV set, and then into Andrew, creating a fatal air embolism. Andrew gasped and died instantly.

When the resuscitation effort failed, shocked hospital staff set in motion the institutional procedures for notifying a family of a child's unexpected death. Although the resuscitation effort had disrupted the physical scene around the child's bed, the improperly connected tubing remained in place, and interviews with nurses

and therapists provided a clear picture of the circumstances. Also, later review of a chest X ray taken during the resuscitation (to check emergency placement of a tracheal tube) found air disseminated throughout many of the major blood vessels. This indicated that the suspected air embolism was indeed the mechanism of death.
Devices involved: IV set and tubing; nebulizer and tubing; video wires.
Proximate cause: Use error: failure to connect tubing correctly.
Institutional/system factors: Inadequate professional training and institutional reinforcement about fundamental importance of tracing tubing and electrical connections from origin point to patient.
Design factor: Tubing connectors that allow incorrect connections; failure to prominently label tubing that is not protected from incorrect connections.
Other comment: Mandatory standards for tubing connector design are not in place.
Further reading: ISMP (2003); ECRI (2004b).

Vignette O: Fatal incubator malfunction. *The total dependency of infants requires that pediatric devices have redundant safety mechanisms. In this case, an infant incubator overheated, resulting in the death of a baby. The noisy, busy environment of the neonatal intensive care unit contributed because nurses did not hear the device's alarm.*

Brittany, a 2-week-old newborn in the intensive care nursery of a hospital, was resting inside of the protected world of her isolette (incubator). Within this world, all vital environmental variables—oxygen, humidity, heat, and light—are fixed to support a fragile baby's existence. The nursery was understaffed and, as usual, it was noisy with many alarms, infant cries, telephones, and beeping monitors. Brittany's isolette alarm went off, but none of the nurses noticed. The alarm was, in effect, cognitively "subtracted out" by similar incoming auditory stimuli. Eventually, a nurse noticed that the isolette display showed an abnormal blanked-out reading. When found, Brittany had suffered irreversible, fatal hyperthermia (excessive body temperature). The isolette had malfunctioned and had gotten so hot that the mattress tray had melted.

The facility and the manufacturer initially could not determine the source of the problem, and a literature search turned up no

similar events. Consultant engineering specialists eventually determined that a brief power interruption had disrupted computer control of the device, which produced an abnormal display and allowed the fatal overheating. The power interruption had been caused by loosened wires within a replacement power plug on the device's power cord. The replacement had occurred before the unit was shipped to the hospital. The investigators also found that the high temperature back-up thermometer had been improperly serviced by the manufacturer. In another critical failure, the hospital engineering staff had not conducted the usual incoming inspection of the device after a communication error left them unaware that the device had arrived. The hospital risk manager reported the incident to FDA and the manufacturer. The manufacturer, after filing two reports that the investigation was continuing, filed a third report that described the wiring problem.

Some time after Brittany's physician had told her family the shocking news of the baby's death and offered support for the family in their grief, the physician and other hospital personnel—consistent with institutional policies and procedures and with help from the family services unit—met with the family again. They again expressed their deep regrets, but they also described what they had learned, explained what they were doing to prevent such a tragedy from occurring again, and answered the family's questions. Later, the hospital and the family agreed on a financial settlement, which was followed by a settlement with the manufacturer.
Devices involved: Incubator, back-up thermometer, detachable power cord, skin temperature probe.
Proximate cause: Manufacturing error in installing power cord; improperly adjusted back-up thermostat.
Institutional factors: Failure to conduct initial product inspection; communication failures; environmental noise; understaffing.
Further reading: Adapted from FDA (2002n, Case Study 8).

SOURCES OF ADVERSE DEVICE EVENTS

The stories above illustrate many sources of adverse device events and close calls. Box 4.2 presents one categorization of event sources and provides brief additional examples of each.

The critical source of an adverse device event may be as profound as a shortfall in basic scientific understanding of a disease or physiological process, for example, the long-term effects of incubator-supplied oxygen on

BOX 4.2
Possible Sources of Adverse Device Events with Examples

Science/evidence base or engineering concepts
- Blindness associated with original use of high-dose oxygen therapy for infants without controlled study of effects
- Unexpected intensity of calcification of tissue heart valves in children revealed during long-term patient care
- Failure of nebulizer devices to produce particles of therapeutic drugs that reach infant lungs

Device design (including design of accessory devices and software)
- Specification of type or grade of material not adequate for a component's intended or reasonably foreseeable uses and environments
- Off/on switch for home use device that is inadequately protected from unintentional activation or deactivation by child patients or siblings
- Design of tubing connectors that allows crossing of fittings or connections for oxygen and other gases in surgical suite or ICU
- Flaw in software that allows data entry error to go undetected

Manufacturing process
- Failure of sterilization procedures that allows contaminated device to be shipped
- Substitution of inadequate for adequate material or grade of material
- Installation of wrong computer chip to control a device function
- Improper connection or wiring of device parts during assembly

Labeling
- Failure to provide instructions about safe and appropriate use of a device in language that is understandable to parents, other caregivers (e.g., grandparents), or children who will use the device
- Undue reliance on labeling as a means of educating clinicians, parents, and patients about safe and effective use of a medical device

User facility administrative and patient safety systems
- Inadequate policies and procedures for purchasing safe and appropriate devices
- Inadequate systems for monitoring and responding to recalls, safety advisories, and other warnings

continued

children's eyes or the interaction between a child's body and a material used in a device. The source may also be as ordinary as a typing or data entry error for a programmable device, an error which, although mundane, can have tragic consequences for an individual child and family. One goal of human factors engineering and other safety strategies is to design devices and the systems in which they are used in ways that either limit the oppor-

BOX 4.2 Continued

- Inadequate provisions for communication with patients and families about how to prevent, identify, and correct or report device problems
- Understaffing

User facility device inspection and maintenance
- Inadequate inspection of newly purchased device to detect defects
- Failure to follow recommended maintenance schedule for device
- Use of improper maintenance procedures

Environmental conditions at site of use
- Electrical power failures with no or inadequate backup power source
- Susceptibility of cardiac and other monitoring devices to electromagnetic interference from digital television signals
- Noise levels in neonatal intensive care unit too high for equipment alarms to be heard

Operator/user training and supervision
- Clinicians performing complex new procedure without sufficient training and monitoring ("learning curve" problems)
- Change in use characteristics of a common device that is not adequately communicated to operator/user
- Insufficient education and assessment of patient or family member understanding of their responsibilities for safe and effective device use in the home or community

Device operation by individuals or teams
- Use of shortcuts, workarounds, or other practices that depart from labeling directions
- Parts of device or device and accessories incorrectly assembled by user
- Failure of user to set or program device correctly
- Inappropriate reliance on an alarm or other automated feature of a device

Tampering, sabotage, or counterfeiting
- Marketing of counterfeit nonabsorbable polypropylene mesh (3" × 6") used in the repair of hernias

SOURCE: A starting point for the categories used here was the classification scheme devised by ECRI for its Medical Device Safety Alert database (see http://www.mdsr.ecri.org/); see also Bruley, 1994; FDA, 2002n; ECRI, 2005.

tunity for certain types of use errors or block them from having harmful consequences.

Compared to drugs, use errors tend to be much more variable in nature for devices, reflecting the greater physical diversity of medical devices and their means of human use. Some adverse drug events actually stem from errors in the use or design of medical devices, for example, infusion pumps.

A device problem may sometimes be quite obvious. For example, a medical device may visibly warp or crack. Certain kinds of use errors, such as faulty connection of tubing, may also be quickly evident. In this respect, the proximate cause of many device adverse events may be clearer than with many events involving drugs, including those involving interactions with other drugs.

In other cases, extended investigation may be required to determine that a bad outcome or adverse event is related to a medical device. Infections, which can have many possible causes, are a case in point. A device-related infection (e.g., one associated with a design flaw or deficient sterilization practices) may only be suspected when an unusual pattern or trend in infections is noticed and other explanations appear inadequate. Linking the infection to a medical device can require combination of laboratory and epidemiological studies, as was the case with the earlier story (vignette N) about infected bronchoscopes (see also the investigation of meningitis in patients with cochlear implants discussed in Chapter 6).

Sophisticated devices with many different components present particular challenges for adverse event investigation. A recent article on the possible hazards of telemedicine used a number of adverse event reports in MAUDE to illustrate how incidents involving complex, software-controlled technologies (which often integrate components from several manufacturers) can be extremely difficult to understand, recreate, and diagnose (Johnson, 2003; see also Johnson, submitted for publication).

As noted throughout this report, although adverse device events sometimes have single causes, they often have multiple contributing factors. In addition, events often involve multiple devices (and multiple people interacting with the devices), each of which may need to be evaluated as a possible cause or contributor.

A few studies of adverse events and medical errors have looked at pediatric populations. For example, an analysis of voluntary, anonymous reports to a network of neonatal intensive care units reported 1,230 events in a 27-month period (Suresh et al., 2004). Nearly half of the errors resulted from failures to follow policies or protections and approximately a quarter each from inattention and communication problems. During the last 10 months of the study period, 2 percent of the events resulted in serious harm and 25 percent in minor harm. Another study reported that a complication related to medical care was found with 0.8 percent of all hospital discharges of children in 1996 (McCormick et al., 2000). A more recent analysis of a large database of inpatient admissions from 1988 to 1997 found rates of hospital-reported medical errors between 1.81 and 2.96 per 100 discharges (Slonim et al., 2003). Rates were significantly higher for technology-dependent or special needs children, a finding consistent with studies of adults.

LIMITATIONS OF ADVERSE EVENT REPORTING PROGRAMS

Problems with the passive or spontaneous reporting of adverse events or health problems are hardly unique to medical devices or FDA programs (see, e.g., O'Neil et al., 1993; Cullen et al., 1995; IOM, 2000c, 2004b; Wald and Shojania, 2001b; Samore et al., 2004). Other public health agencies, medical product manufacturers, health care facilities, and patient safety organizations experience similar problems. Notwithstanding the limitations, event reporting remains an important component of existing and evolving programs to protect patients and improve public health.

FDA's program for the reporting and analysis of adverse device events has been the subject of at least three reports by the Government Accountability Office (GAO, formerly the General Accounting Office). The first two, issued in 1986 and 1989, reported significant weaknesses (GAO, 1986, 1989). A 1997 report credited FDA with improvements (some in response to legislative changes) but stated that "FDA does not systematically act to ensure that the reported problems receive prompt attention and appropriate resolution" and thus does not function satisfactorily as an early warning system for problem medical devices (GAO, 1997, p. 2). The report also cited the agency's slow review of reports of device malfunctions that did not result in harm but that might nonetheless have served as early warnings of problems before they caused harm. In 2003, FDA itself characterized its program of postmarket surveillance as "not working well" (FDA, 2003n, unpaged).

In addition to criticizing FDA, the 1997 GAO report also criticized the quality of user facility reporting. It cited delayed reports, failure to submit semiannual summary reports, and lack of critical information (e.g., type of device, outcome of event). It proposed that feedback to reporting facilities of information about the outcome of a report might improve knowledge of device problems and encourage better reporting. The report acknowledged the agency's response that providing such feedback would require substantial resources. As described below, the pilot MedSun program responds to some of the GAO's criticisms by providing more feedback and other interaction with personnel at participating facilities.

A recent estimate of underreporting of medical device-associated adverse events came from an analysis of data from National Electronic Injury Surveillance System (NEISS), which has information on consumer product-related injuries based on emergency department records from a probability sample of hospitals (Hefflin et al., 2004). The analysis found the number of reports was "four times greater than the annual number of adverse event reports received by medical device-regulating surveillance systems" (Hefflin et al., 2004, p. 246). This analysis may provide some sense of the magnitude of serious, device-related problems experienced by patients outside the hospital. NEISS does not capture data on injuries treated in other areas of a hospital, which would include injuries associated with device errors or

malfunctions that were, for example, experienced and managed in the intensive care unit.

Underreporting is also suggested when a public health notification or recall brings attention to a problem and FDA then sees a sudden increase in reports of the problem. One example reported in the literature involved a vacuum extractor used to assist vaginal delivery of a newborn (see, e.g., Ross et al., 2000).

The limitations of passive or spontaneous reporting of adverse device events apply generally to both adults and children. It is possible, however, that the events affecting children could be subject to higher or lower rates of underreporting or poor-quality reporting. The committee is not aware of any relevant comparative studies.

Problems with Reporting of Adverse Events

> *"The 'grapevine' system of reporting appears to be relied upon by physicians and other health professionals. In many subspecialties, including cardiology and neonatology, there is a small network of pediatric experts. It is common for these physicians to share stories of mishaps or near misses in an effort to prevent others from making the same mistakes. This dependence by many individual physicians on this kind of information sharing is clearly not sufficient. . . . [However,] there is no quick, simple system to allow reporting of medical device usage (both successful and unsuccessful). Current electronic databases [of adverse reports] are often difficult to locate and can be cumbersome or time consuming to use."*
>
> American Academy of Pediatrics (AAP) et al., 2004b

Important as informal professional communication networks are, they are not adequate to the task of systematically identifying and communicating the array of problems that can arise with the design, production, distribution, and use of medical devices. Such networks also are not universal and may not reach those clinicians or other users most in need of information about problems with medical devices. Furthermore, although informal communications may lead to alterations in professional practice, they may or may not reach hospital risk managers, device manufacturers, FDA, or others in a position to respond more comprehensively to device problems once they are identified. In some respects, informal communication might be viewed as a "workaround," a way of compensating for some of the inadequacies of formal surveillance programs.

Contributors to Underreporting

Several of the vignettes presented earlier in this chapter described failures to report adverse events and also suggested some of the reasons for

underreporting. In addition to ignorance of reporting requirements or opportunities, reasons include workload pressures, liability considerations, misunderstanding of privacy regulations, concerns about competitors, and lack of adequate institutional procedures and other support for reliable reporting.

As users of devices, clinicians may not be aware that devices are "reportable" products and that FDA has an adverse device event reporting program. Clinicians also may be accustomed to "working around" certain kinds of device problems without recognizing them as reportable events (AAP et al., 2004b; Bright, 2004).

At the institutional level, patient safety programs have tended to focus more on medication errors than device errors. Institutions have been slower to develop structures and procedures to support the reporting, understanding, and prevention of adverse device events, including education of clinicians about their role in identifying adverse device events and device malfunctions or failures. Institutions may likewise lack reliable mechanisms for learning about and implementing device recalls and public health notifications that advise changes in practices involving a device.

Some institutions have been intimidated or confused by the patient privacy provisions of the Health Insurance Portability and Accountability Act of 1996 (HIPAA, P.L. 104–191). On its MedWatch website, FDA has clear messages that "the Privacy Rule specifically permits covered entities (such as pharmacists, physicians, or hospitals) to report adverse events and other information related to the quality, effectiveness, and safety of FDA-regulated products both to the manufacturers and directly to FDA" (FDA, 2003b, unpaged). In addition, the Privacy Rule permits (but does not require) covered entities to disclose—without getting a patient's authorization—protected health information to parties (for example, manufacturers) that are conducting postmarket surveillance required by FDA (45 CFR 164.512(b)(1)(iii)(D)). (State laws can be more conservative than federal law, but most are consistent with respect to public health exceptions.)

It is the committee's sense that confusion about HIPAA and the legal discretion of user facilities and professionals to disclose patient information related to adverse events to FDA or manufacturers remains a problem. The actual instructions for Form 3500A for reporting adverse events do not mention HIPAA, although MedWatch has a notice about HIPAA that is displayed on the page that includes links to forms and information about reporting safety problems. As discussed in Chapter 6, HIPAA also is a concern for manufacturers and investigators collecting information for required postmarket studies.

When health care professionals and institutions do report adverse device events, they do not always include essential information about the event, the device (e.g., specific model), and any attached accessories. Front-

line clinicians may know little or nothing about the history of a device (e.g., whether it has been refurbished), and they may not be aware of the difference between a device brand and a specific device model. If not documented at or near the time of an event, these kinds of details may be difficult to reconstruct or collect later. Details about generic, seemingly innocuous products such as many kinds of tubing may be practically unavailable.

In addition, concerns about liability related to possible errors in the use of a device may affect whether professionals and user facilities report a problem, how they characterize the nature and source of the problem (e.g., use error versus design problem), and whether they provide a manufacturer with a device for evaluation.[3] This concern exists despite the confidentiality protections offered by FDA's statute and regulations for patients, physicians, and other initial reporters of events, and (in most situations) user facilities (21 USC 360i(b)(2); 21 CFR 803.9; 21 CFR 20.63(f)). Identifying information about these reporters is not included in the public MAUDE database, and such information in the internal FDA database is not releasable in responses to requests under the Freedom of Information Act. Internal facility records documenting an adverse event and its investigation are not so protected.

In contrast to user facilities, the names of manufacturers and devices are included in the public MAUDE database. Such information is a necessary means of identifying problems with specific devices (including use errors) and disseminating that information to clinicians, user facilities, and patients. Anonymous reporting, which may be constructive for some purposes, is not appropriate in this case. Notwithstanding regulatory requirements and public health arguments, manufacturers may understandably be concerned that their reports will attract attention from lawyers who specialize in medical product and malpractice litigation (see, e.g., Quinley, 2001).

Moreover, competing companies have access to the public MAUDE reports. One long-time observer of medical device regulation suggested that competitive pressure "is a powerful deterrent [to reporting events], leading companies to file no more than the least amount necessary under a law—

[3]MedSun training materials distinguish between accident (adverse event) investigations and forensic investigations. "The goals of an accident investigation are to determine what happened, why it happened, and which corrective actions and preventive measures can be taken. The goal is not to assign blame. . . . Forensic investigations are performed in relation to litigation, arbitration, and contract issues. . . . [The goal] is to provide a clearly stated, reasonable biomedical engineering or medical opinion on the cause of the accident at deposition or trial. . . . Some investigators see the assignment of blame as one fundamental goal of a forensic investigation. In this regard, however, it is important to remember that in the end, legal liability is determined by juries and courts" (FDA, 2002n, p. 3-2).

especially since these reports can be read selectively" (Dickinson, 2004c). Both liability and competitive considerations create incentives for manufacturers to interpret an adverse event as resulting from user error rather than to cite device design, labeling information, and similar factors that might have caused or contributed to the event.

Overreporting

Although the discussions of problems with adverse event reporting systems tend to focus on underreporting and incomplete reporting, what might be called overreporting is also a problem. That is, user facilities, health care professionals, and consumers may report events that are not related to a medical device (or its use) but rather to the patient's underlying medical problem or some other circumstance. They may also report trivial events. FDA has provided guidance to user facilities and others about what not to report, but it is obvious from a scan of recently submitted reports that the advice is not always followed. In 1993, FDA concluded that of approximately 2,834 reports it received from user facilities, only 664 should have been submitted (cited in GAO, 1997, p. 17).

Inappropriate reporting adds to the burden on FDA staff and on the manufacturers who initially receive most adverse event reports that are submitted to FDA. Manufacturer complaint files include many reports that are screened out as not reportable.

Shift of Care from Hospital to Home

Several of the vignettes presented above involve a particular patient safety challenge—the shift of complex care from the hospital to home. This shift reflects, in part, the progress in biomedical science and engineering that allows more adults and children, first, to survive severe medical problems and, second, to live at home with supportive technologies. Little information is available about medical device safety or adverse events in the home (see, e.g., CHCPR, no date; Lantos and Kohrman, 1992; AAP, 2000b; Tucker, 2004; Bruno and Ahrens, 2005).

Pediatric home health care is, essentially, a stepchild in patient safety programs. The movement of care and devices out of the hospital has not been matched by programs to encourage the awareness, documentation, investigation, and reporting of adverse device events. In the committee's experience (including its discussions with parents), many if not most patients and families are likely to be unaware that FDA has a role in device safety and provides for written or online submission of problem reports from consumers. The committee found virtually nothing about the reporting of adverse events by home health agencies, which may not be even

aware of events and may, in any case, focus exclusively on resolving problems (e.g., clarifying operating instructions for families, troubleshooting problems, swapping out malfunctioning devices) without regard to their legal responsibilities for event reporting.

Recognizing that medical device safety in the home is a neglected area, CDRH has created a home health care committee. Among other resources, the committee has created a checklist that provides useful, basic guidance in relatively nontechnical language for families or patients using medical devices at home (FDA, 2003l). The major checklist headings advise

- As a homecare medical device user, you should know how your device works.
- Take care of your device and operate it according to the manufacturer's directions.
- Always have a back-up plan and supplies.
- Educate your family and caregivers about your devices.
- Keep children and pets away from your medical device.
- Contact your doctor and home health care team often to review your health condition.
- Report any serious injuries, deaths, or close calls.

A number of organizations have endorsed the FDA checklist, and it may be freely copied and distributed by professional societies, patient advocacy groups, and others. The committee encourages its wider distribution, especially by groups such as the American Academy of Pediatrics and the National Association of Children's Hospitals and Related Institutions that are involved with technology-dependent children.

Identifying, Documenting, and Investigating Possible Adverse Events

The identification, reporting, and investigation of adverse events, device problems, and close calls is an important task that is most reliably performed in the context of clearly defined organizational structures and procedures maintained by manufacturers, health care providers, FDA, and other relevant organizations (e.g., engineering consulting groups). Individual patients and families at home and even office-based physicians and nurses are, in general, not well prepared to investigate such events, even if they recognize them as possibly related to a problem with a device or its use. Within health care institutions, well-functioning quality management and patient safety programs should ideally provide a culture that supports the recognition, reporting, and investigation of device safety problems as well as procedures that make it easy to do so. (It is not clear that this observation applies to home health agencies that are not well integrated into the culture

of a larger health care organization that has strong patient safety programs and norms.)

Figure 4.1 depicts in a simplified form the basic steps to be followed in a hospital or other facility once an obvious or possible adverse event (or close call) is recognized. The figure highlights the importance of documenting the circumstances of an event and maintaining the scene until a preliminary investigation can be conducted. In some cases, investigations are

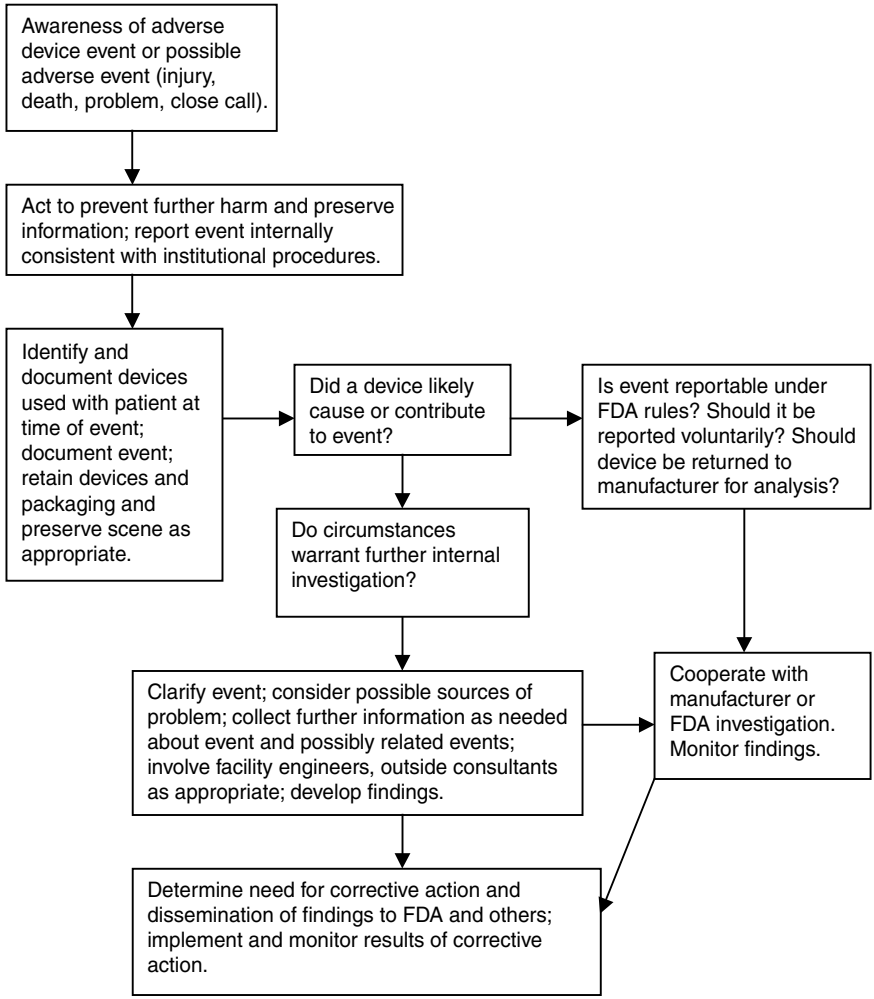


FIGURE 4.1 Identifying and investigating an adverse device event in a health care facility (adapted from MedSun training materials [FDA, 2002n]).

hindered because a device or its key accessories are not available for examination or the device has been cleaned or changed in some way (e.g., its electronic memory erased) that eliminates or compromises relevant information. An important feature of the MedSun program is training in procedures to follow after an event is recognized (e.g., properly impounding and storing devices involved in an incident and otherwise securing and protecting the integrity of relevant materials, records, and information).

Even when a problem with a device is obvious, for example, when a device has fractured, the contributing factors may not be obvious. A fracture could result from a design flaw, a short-term manufacturing lapse, use of the device outside its specifications or directions for use, or other causes or combination of causes. It may be impossible later to identify the source of an adverse event or close call if the setting and circumstances surrounding the problem have not been carefully and accurately documented and if the device and related packaging and accessory devices are no longer available for analysis. Documentation is a particular concern with events that occur in home settings where family members rather than professionals are primarily responsible for the day-to-day operation of devices.

Manufacturer examination of retrieved devices is often useful in determining whether and why the device failed or malfunctioned or whether a design feature contributed to a user error.[4] Implant retrieval, however, faces a number of obstacles, including confusion about the ownership of a device, provider fears of liability, provider emphasis on fixing problems, costs of retrieving and returning devices, and lack of formal procedures for obtaining patient consent. A 2000 NIH document stressed the importance of device retrieval for device research and recommended that the information card for patients with implants provide an opportunity for patients to consent to implant retrieval (NIH, 2000).

To the extent that documentation of the circumstances of an adverse device event depends on information from the patient, some details may not be available when the patient is an infant or very young child. (Limits on communication with infants and young children may also contribute to adverse events, for example, when children cannot provide important information about what they are experiencing or when fear interferes with their ability to cooperate with a procedure.) Participants may also provide incon-

[4]To cite one recent case, as part of its program to analyze products returned from physicians, one company identified a small number of implanted defibrillators that had a battery shorting problem that could lead to rapid battery depletion (Medtronic, 2005). Based on additional testing, the company estimated that perhaps between 0.2 percent and 1.5 percent of the devices in question could develop the problem. Using its registry information for the devices, the company provided physicians with a list of possibly affected patients.

sistent accounts of an event, and those recording or investigating these accounts may introduce inaccuracies or biases that complicate the search for causation. As noted above, liability and competitive concerns also have the potential to bias reports.

The initial focus of adverse event investigations is on identifying the immediate circumstances and causes of an event, for example, a use error or manufacturing flaw. Human factors analysis and root-cause analysis go beyond the immediate or proximate source of an adverse event to identify underlying and potentially preventable device, use, environmental, and other organizational or systems factors that contributed to the event (see, e.g., Sawyer, 1996; Murff et al., 2001;Wald and Shojania, 2001b). As described below, human factors analysis can also be used prospectively to identify and avoid device design features that promote use errors.

Determining Whether a Problem Exists

Although it is important for those immediately involved in an adverse event or other problem involving a medical device to take the steps identified above and to assist in a health care organization's investigation of the event, the organization itself may not have the critical expertise needed to evaluate an event or problem. Often, that expertise resides with the manufacturer of a device. In some cases, health care organizations or manufacturers may call on outside engineers or other consultants for assistance and confidential evaluations of a problem or potential problem with a device.

As noted above, the nature of an adverse event, malfunction, or other problem associated with a device is sometimes such that those involved can feel reasonably confident that a device problem exists, for example, that the packaging is faulty or that the device has arrived with an element incorrectly assembled. The primary questions then focus on the extent of the problem (e.g., certain lot numbers or all lot numbers) and its origin (e.g., a single random manufacturing aberration, an aberration affecting several product lots, a problem with an accessory device, or a design characteristic that becomes a problem only in unusual circumstances).

In other cases, it may be much more difficult to link an unwanted outcome (e.g., an infection or a surgical injury) to a problem with the device. The outcome may be one that can occur as a result of the patient's medical condition or that is a known risk of treatment for the condition.

When adverse events are analyzed, one question is whether the type of event is occurring uniquely or more frequently among patients who are treated with a particular medical device. As discussed further in Appendix D, answering this question requires data about both the frequency of the event in question (numerator data) and the population with and without the device who are potentially at risk of the event (denominator data).

Ideally, additional information would also be available about other patient characteristics (e.g., age, gender, severity of illness) that might affect the likelihood of the event. Adverse event databases suffer deficiencies in all these areas.

Further, because underreporting, incomplete reporting, and biased reporting are such severe problems with passive adverse event reporting systems, it is expected that reported instances of a particular device-associated event will typically be only a fraction of all instances of the event. Underreporting and the lack of comparative population information necessary to construct event rates are important reasons for the interest in surveillance based on large automated population databases such as those of big HMOs

For some devices, it may be possible to make estimates for some missing variables using information from the manufacturer, for example, device tracking registries or registries created as a condition of marketing approval. Other registries such as those created by professional groups or academic medical centers may likewise be useful in making estimates. FDA analysts may also seek data on adverse events from public health databases, as in the investigation of meningitis cases among recipients of cochlear implants cited above and discussed in Chapter 6.

In addition, data from premarket clinical studies may be evaluated. A case in point involves reports of subacute thromboses and possible hypersensitivity reactions following introduction of a drug-eluting stent. In October 2003, FDA issued a public health advisory on the topic. A month later it issued another notice stating that the agency's review of pre-approval clinical trial data indicated that the rate of subacute thromboses was the expected rate for such stents and that many of the hypersensitivity reactions may be related to the drug therapy associated with the stenting procedure (Alonge, 2004).

Improved epidemiologic research capacity would help the agency tap alternative information sources. FDA funding restricts the time that analysts can spend both reviewing reports of serious adverse events and investigating those reports that are suggestive of a problem with a device or its use.

Responding to Problems

As described in several vignettes above, the most immediate response to an adverse event may be rescue interventions undertaken by health care professionals (or parents at home). In some cases, the event may prompt no investigation. In other cases, an affected institution may identify a problem with a device and take action to change or restrict the use of the device, perhaps without reporting the problem to either the manufacturer or FDA. Such isolated responses deprive other patients and physicians of potentially valuable safety information, although professional communication net-

works may disseminate information about the problem and the response, which, in turn, may lead to action in some other institutions.

Reports to manufacturers and FDA allow wider communication of problems. As reported by GAO, an FDA analysis found that approximately 25 percent of all classified device recalls were linked to adverse event reports, but about half of recalls involving Class I devices were associated with such reports (GAO, 1997).

In some cases, a single incident report or even a close call may be sufficient to prompt a response. For example, in 1985, an infant was electrocuted when a sibling connected the electrode lead wires for the child's apnea monitor to a power source (cited in GAO, 1997). FDA issued a safety alert and asked all manufacturers of home apnea monitors to evaluate their devices to determine whether changes were needed. The agency subsequently changed the criteria for clearing new devices to require that devices be designed to protect against this risk. Eventually, it issued warnings to hospitals about the continued use of devices with unprotected leads that were sold before the change in clearance criteria was applied to hospital monitors (FDA, 1993a).

Chapter 3 identified several short-term responses available to FDA and a manufacturer once a problem with a device is identified. These responses range from developing warnings or advice for practitioners to recalling a product. Table 4.3 summarizes such responses to device problems for the years 1998 to 2004.

TABLE 4.3 Medical Device Class I Recalls and Safety Alerts, Public Health Advisories, and Notices, 1998–2004

	1998	1999	2000	2001	2002	2003	2004
Class I Recalls	5	7	16	9	11	14	28
Web Notifications	0	0	0	0	3	3	3
Public Health Advisories, Notifications, Notices, Letters, Safety Alerts, and HHS News Items	17	12	4	6	6	4	2
Talk Papers	1	0	0	0	0	1	0
FDA Press Release	2	1	0	0	0	1	11

NOTES: The reference to Safety Alerts, Public Health Advisories, and Notices in the title is taken from the FDA title for this information in the main FDA safety page (FDA, 2005d). Labels for these notifications have changed over time.

Updates for safety notices are counted as original notices. Most press releases cover recalls that are also reported in the first line of the table.

SOURCE: FDA Medical Product Safety Information (FDA, 2005d) (cited May 11, 2005), FDA CDRH Public Health Notifications (FDA, 2005h) (cited May 11, 2005), and ECRI Health Devices Alerts Database. FDA lists Class I, II, and III recalls in its monthly Enforcement Reports (see FDA, 2005b).

As noted earlier, adverse event reports can direct attention to problems with the design of a device and, thus, provide opportunities for device refinement or innovation. Not surprisingly perhaps, manufacturers' responses to adverse event reports as found in MAUDE usually provide no indication that they might be considering a report as a resource for evaluating device design.

The committee did not investigate FDA procedures for issuing and following up on safety alerts, but it does have some concerns about whether FDA has adequate resources to analyze adverse event reports and to develop responses for problems that are not seen as high-priority but that nonetheless may pose real risks to children in particular. The problems with orthodontic headgear are a case in point. In a November 2004 story on a child blinded by a mishap with orthodontic headgear, a Washington, D.C., television station criticized FDA for not having taken any action to protect children although FDA staff acknowledged that they were aware of the problem (WTTG, 2004). A search of FDA databases yielded three reports of headgear-related eye injuries (in 1990, 1997, and 2002) as well as additional reports related to other problems, including device breakage. Reports of blinding injuries have also appeared in the literature for at least 30 years (see, e.g., Samuels et al., 1996; Blum-Hareuveni et al., 2004). The American Association of Orthodontists presented guidelines and cautions on the use of these devices in 1975, but apparently has not revisited the issue since then (AAO, 1975). A committee inquiry to FDA found an investigation of headgear injuries had been initiated, and in spring, 2005, an article on headgear safety appeared in *FDA and You*, an online publication for health educators and middle and high school students (FDA, 2005c). It is not clear whether further dissemination may occur to get this information before those facing decisions about the use of orthodontic headgear (personal communication, Thomas P. Gross, M.D., Director, Division of Postmarket Surveillance, CDRH, June 3, 2005).

One likely reason that the headgear-related risks have not attracted more attention is that the devices have been used by millions of children with few reports of injury. These products are also not as attention getting as more "high-tech" devices such as implants. Furthermore, headgear injuries and other incidents typically occur at home and, if not severe, they may be treated by office-based practitioners who are not required to report adverse device events and are likely unaware of voluntary reporting options. Emergency room physicians who treat serious injuries associated with these and other medical devices may likewise be unaware that they can voluntarily report events to FDA. Nonetheless, the long and continuing history of headgear incidents and the rare but devastating injury raise questions about whether lack of resources has limited FDA's ability to investigate and respond.

FDA has been more attentive to the problems with circumcision clamps as described in Box 4.1 and Vignette A. A few years ago, CDRH analysts noticed a large enough number of lacerations and other events related to the clamps (105 reports of injuries between July 1996 and January 2000) that it undertook an investigation that led to a safety alert in 2000 (FDA, 2000g). Subsequently, reports of injuries dropped, but the agency was concerned that incidents were still occurring and being reported, so it reiterated its warning in an item in its Patient Safety News series in 2002 (FDA, 2002a). The FDA warnings on circumcisions clamps followed—and cited—several earlier notices by ECRI, a private nonprofit technology assessment and health care research organization (see ECRI, 1993, 1995, 1997, 1999, and discussion at end of this chapter).

Public health notifications are not sufficient responses to some device problems. Recalls of a product may be necessary. Whether a recall is undertaken at a manufacturer's own initiative, as a result of an FDA request, or after an FDA order (which is rare), the recall will not reach its goal of protecting patients if information about the recall does not get to those who need it. The same observation, of course, holds true for dissemination of information about labeling changes or new advice about the appropriate use of a device.

FDA recognizes weaknesses in the recall process. As summarized in one overview, recalls can go unnoticed for various reasons, for example, "recall information doesn't get into the right hands, registered letters are sent to old addresses, hospitals don't see notices because they are swamped with so many other responsibilities, or perhaps there are mixed signals on the urgency of the problem" (Rados, 2003, unpaged).

Vignette E cited problems with misrouted information about the recall of a bronchoscope. It noted that hospitals can subscribe to information services that automatically alert them to device recalls and other relevant safety information. FDA's MedWatch program also allows people to sign up for automatic e-mail safety alerts that cover devices, drugs, biologics, and dietary supplements. An alert system limited to devices may, however, make it easier for those concerned specifically about device safety to focus on device problems. In addition to helping professionals evaluate problems and gain insights from peers, listserves and similar tools can also help disseminate safety information.

FDA INITIATIVES TO IMPROVE ADVERSE EVENT REPORTING AND RELATED ACTIVITIES

FDA clearly recognizes limitations of adverse event reporting programs in general as well as particular concerns with its own program. Sometimes with congressional direction, it has undertaken or planned a number of

initiatives to respond to certain limitations and concerns. The MedSun pilot program, the human factors initiative, and other activities described below are examples. For the most part, their focus is general, although some include attention to pediatric issues.

MedSun

Compared to the agency's primary spontaneous or passive event reporting program, the pilot MedSun program was created as a less inclusive but more intensive effort to better identify and understand problems with the safe use of medical devices. The program provides for more attention to close calls, more education of participating facility representatives to improve the level and quality of event reporting and analysis, and more feedback and interaction to determine the nature of device problems and close calls as a basis for preventing future problems and improving patient safety within health care facilities. These educational and feedback features offer incentives for institutional participation that are absent in the traditional program. MedSun now has a waiting list of interested facilities (FDA, 2004a). With the possible exception of certain special studies, the program will not collect denominator data that would allow the calculation and comparison of problem rates.

As shown in Table 4.4, by June of 2005, MedSun had recruited over 350 hospitals, of which 22 were acute-care general children's hospitals and 2 were acute-care pediatric specialty hospitals. These participating facilities

TABLE 4.4 Cumulative Number of Facilities Recruited Into MedSun

	2002	2003	June 2005
Nonpediatric hospitals with 100+ beds	57	167	307
Children's hospitals of any size	2	8	22
Children's rehabilitation hospitals of any size	1	2	2
Nursing homes of any size	8	19	21
TOTAL	68	196	352

NOTE: Nonpediatric hospitals with fewer than 100 beds and other types of facilities such as home health and outpatient clinics are not included. Not all sites that have been recruited have received program orientation.
SOURCE: Personal communication, Thomas P. Gross, M.D., Director, Division of Postmarket Surveillance, CDRH, June 10, 2005. Data provided by CODA, Inc.

constitute about 6 percent of all hospitals and 12 percent of children's hospitals. (Nationally, the United States has approximately 4,900 short-term, nonfederal community hospitals [AHA, 2004] and approximately 160 short-term [nonpsychiatric] children's hospitals [NACHRI, 2003].) The modest overrepresentation of children's hospitals in the MedSun implicitly acknowledges the particular value society places on learning about and protecting the health of its youngest members, even though children are, overall, a generally healthy population.

MedSun also includes 21 nursing homes. It does not include any psychiatric hospitals or federal hospitals. It also does not include independent outpatient centers or independent home health organizations, although some participating health systems include such entities. Participating facilities must agree to participate for at least 12 months, but FDA hopes they will agree to renew annually.

An outside contractor (CODA) manages the pilot program. Its responsibilities include providing assistance to participants on mandatory and voluntary adverse event reporting and receiving and processing mandatory event reports before forwarding them to the manufacturer or FDA or both. The contractor also is involved (with assistance from another contractor) in analyzing and providing feedback on event reports.

MedSun requires participating facilities to designate two staff contacts, one from their risk management or quality improvement area and one from their biomedical or clinical engineering staff. The program provides three hours of training in reporting adverse events or close calls. In addition, the contractor and FDA have organized two conferences for MedSun participants, and they have made or plan to make slide sets on special topics (e.g., pediatrics) available for educational and promotional use in participating facilities. MedSun participants can also request FDA analyses of MedSun or MAUDE reports on device problems.

Another benefit for participating institutions is a newsletter that summarizes adverse event reports received by FDA, presents analyses of issues by FDA staff, and provides other information of interest. From 1992 to 2003, FDA distributed a somewhat similar newsletter for subscribers from all user facilities. Acknowledging resource constraints, the newsletter announced its discontinuation, claiming that it "had finally served its purpose" of providing training, education, and feedback on adverse event reporting (FDA, 2003a). This claim is not convincing given the picture presented in this chapter.

As part of an active surveillance element of the MedSun program, participants agree to respond to periodic rapid response surveys that focus on specific product problems or concerns. For example, 29 hospitals have participated in a 6-month study to identify cases of thrombosis or hypersensitivity reaction that occur within 30 days of implantation of a drug-eluting

stent (MedSun, 2004, p. 2). FDA asked cardiac catheterization laboratories in study facilities to complete surveys at the beginning and end of the study and to complete another questionnaire to report any events involving drug-eluting stents. Results have yet to be reported publicly. FDA has planned similar surveys involving other devices.

The committee is not aware of special surveys that have involved only the children's hospitals in the pilot MedSun program. It has learned that both Child Health Corporation of America (CHCA) and the National Association of Children's Hospitals and Related Institutions (NACHRI) have been working with MedSun to assist the project in gaining substantial input from pediatric hospitals (personal communication, Cheri Throop, R.N., Chief Quality Adviser, CHCA, April 22, 2005). One of the recommendations at the end of this chapter encourages FDA and MedSun participating children's hospitals to serve as a resource for the broader involvement of children's hospitals in device safety.

One recent addition to MedSun is the Medical Device Engineering Network (M-DEN), which provides an interactive query and comment option for participants to share questions, experiences, and advice. The discussions may involve problems or concerns that would not normally be reported to FDA (Crowley et al., no date). Several teleconferences already have been organized on topics of interest to biomedical engineers.

MedSun has only recently approached its recruitment goals, and the program has yet to train representatives from many of the recently recruited facilities. Data collection began in February 2002 (FDA, 2004a). Because the pilot program is still in its early stages, it is not ready for systematic evaluation of its performance in meetings its goals. The committee understands that relatively few reports are being submitted each year, on average, by the MedSun facilities, but no public information is yet available. At some point, a comparison of the reports submitted by participating facilities with those received through the passive reporting system will be needed. The recommendations at the end of this chapter include suggestions for the evaluation plan.

Exploring Computer-Based Surveillance and Improved Device Coding

FDA has been interested in the potential applicability to adverse device events of some strategies being used or tested with adverse drug events. For example, the agency supported a study to compare possible device surveillance strategies and evaluate whether computer-based surveillance could reliably detect device adverse events and hazards, which were defined as "a state of increased risk related to device use" (Samore et al., 2004, p. 333). The study, which was conducted at a large medical center that had experience using computer-based strategies for detecting adverse drug events,

concluded that any of the surveillance strategies it investigated detected only a minority of the adverse events that were identified by the strategies collectively and that each strategy had significant limitations. An update of the first published report on the study is currently being prepared (personal communication, Thomas P. Gross, M.D., Director, Division of Postmarket Surveillance, CDRH, February 4, 2005).

A particular focus of investigators was a "computer-flag" strategy that was embedded in the hospital's computerized patient record system. It involved nurse review of flagged records using a protocol devised in consultation with FDA. The flags were based on "detection rules" for seven categories of events (e.g., complications and hazards related to various types of catheters), and one goal was to identify hazards before they caused harm. This approach yielded more information on adverse events than the hospital's voluntary adverse event reporting system, but it missed some important events. Disappointingly, the positive predictive value of the flags was low, that is, the great majority of flagged events did not, upon investigation, involve a device-related problem or hazard. Thus, its utility for detecting potential problems before they could cause harm was limited.

Nonetheless, the computer-flag strategy—in combination with other tools—helped investigators better understand the clinical environment. "It appeared that the typical health care worker response to a device problem was to fix it or retrieve a new device that worked and then move on, an appropriate solution at the individual patient level but not an effective systems approach" (Samore et al., 2004, p. 333). This observation was reiterated in committee discussions with clinicians.

To consider patient perspectives, investigators conducted a post-discharge patient survey. It found that people focused on simple, common devices that caused discomfort rather than what are normally defined as serious adverse events. Events reported in the survey had no overlap with other reports.

Another strategy—retrospective review of medical records for ICD-9-CM codes[5] that indicate a likely device problem (e.g., code 996.01, mechanical complication due to heart valve prosthesis)—was useful in identifying problems that occurred prior to hospitalization. Still, with ICD-9-CM codes, device problems can only be described by broad category rather than by individual device. Thus, this strategy is not well suited to identify a

[5]The International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) is used in assigning codes to diagnoses and procedures associated with hospital utilization. It is based on the World Health Organization's International Classification of Diseases, Ninth Revision (ICD-9). In the United States, the National Center for Health Statistics and the Centers for Medicare and Medicaid Services have responsibility for maintaining the system.

particular device model or brand for analysis of problems in its design, manufacture, or use.

As discussed further in Chapter 6, whether for written or electronic records, a fundamental problem is the lack of an accepted, feasible coding system for devices that is equivalent to that for drugs and allows recording of sufficient device-specific information in the medical record. Chapter 6 includes a recommendation on the development of common standards and approaches for capturing use and outcomes data for implants and other medical devices. Building on extensive experience with device coding and its limitations, FDA recently held a conference to explore new strategies for improving device coding.

Human Factors Analysis

FDA's work in the area of human factors analysis supports steps to prevent device problems and to analyze problems once they occur. As described in Chapter 3, the field of human factors engineering focuses on how people use technologies and how human characteristics (e.g., cognitive capacities, expectations, and physical limitations) interact with characteristics of products and work environments. FDA has been interested in the application of human factors analysis to medical device safety since the 1970s, and its human factors program has worked with manufacturers on the incorporation of human factors engineering principles in the design of medical devices (see, e.g., Carstensen, 1996; Gross, 1996; Sawyer, 1996; FDA, 2000b).

Human factors analysis can also contribute to improvements in the evaluation and characterization of adverse events. One recent activity involved the development of a model for this purpose based on literature review and interviews with device users, primarily nurses (Kaye et al., 2003). The preliminary model defined several broad contributors to device problems related to unmet user needs (e.g., device does not indicate when it is operating improperly), user perceptions (e.g., monitor display is not easy to see), user cognition (e.g., device operates differently from most similar devices), and user actions (e.g., device can be improperly connected to other devices). These categories, which emerged from interviews, include many situations that give rise to the kinds of workarounds described in this chapter and Chapter 2.

Additional Activities

Another FDA initiative is the use of Systematic Technical Assessment of Medical Products (STAMP) teams to examine adverse events, including deaths and serious injuries, associated with selected devices (FDA, 2004v).

Teams, which include experts outside FDA, have examined surgical staplers and clips and laparoscopic trocars (devices that penetrate the abdomen and pelvis to allow insertion of laparoscopes and surgical instruments). The first such examination focused on shunts used with hydrocephalus (FDA, 1999f).

The agency also participates in the Quality Interagency Coordination (QuIC) Task Force, a department-wide patient safety initiative. One study in this context has audited Medicare patient records to identify certain events (other than infections) related to central venous catheters. In initial findings, the devices were associated with a 2 percent rate of events such as misplacement of the catheter or pneumothorax (air or gas in the space surrounding the lungs, often called a collapsed lung) (Gross, 2004).

OTHER REPORTING AND ANALYSIS OF ADVERSE EVENTS

Beyond the activities of health care facilities, manufacturers, and FDA as described above, it is worth noting that a number of other public and private programs include the reporting and analysis of adverse events as part of broader health care quality and patient safety programs. Notable among other federal agencies is the program overseen by the National Center for Patient Safety of the U.S. Department of Veterans Affairs (http://www.patient.safety.gov). Examples of one state and two private programs are briefly described below. Most patient safety programs do not emphasize adverse device events as such.

State Reporting Program: New York

A number of states, including New York, Pennsylvania, and Oregon, have created some form of adverse event or patient safety reporting program. New York State has required since 1985 that hospitals report certain types of adverse events. In 1998, it required a more comprehensive, Internet-based system—the New York Patient Occurrence and Tracking System, or NYPORTS (Hevesi, 2003; see also New York State Department of Health, 2004). Under the program, covered facilities are to report the most serious incidents or "occurrences" within 24 hours.

Of 54 defined types of incidents, the program has classified 19 as "most serious," including unexpected patient deaths and equipment malfunctions that result in patient harm. Facilities are to investigate and report on the causes of the incidents within 30 days using a standard investigation and reporting format, which should document a root-cause analysis of the occurrence. (Hospitals can report information electronically, but the state's diagnostic and treatment clinics cannot.) The state Department of Health uses the data for a variety of quality improvement and patient safety purposes.

The New York program is more comprehensive than FDA's medical product reporting in that it covers problems not related to medical products, for example, surgery on the wrong patient or wrong part of the body. In contrast to MedWatch, which focuses on manufacturer analysis of problems, New York puts more demands on facilities to investigate and report incidents in a systematic fashion that supports problem identification and quality improvement activities. Information is shared with facilities, but individual reports are protected from public disclosure. The New York program thus has some features in common with FDA's pilot MedSun program.

One problem that the New York program shares with FDA is underreporting of events. A recently released audit of the program documented underreporting of serious events and late or missing investigation reports of serious occurrences (Hevesi, 2003). Of the nearly 5,800 reports that the audit said should have been reported within 24 hours, 84 percent were not.

Private Reporting Programs

A variety of other private organizations concerned with health care quality and patient safety include some attention to safety problems with medical devices. For example, the Institute for Safe Medication Practices has described hazards linked to the design or use of medical devices used to administer medications. Patient safety and quality improvement initiatives sponsored by consumer groups such as the National Consumers League and professional societies such as the American College of Cardiology (ACC) and the American Thoracic Society may likewise cover device issues. For example, the ACC was a joint sponsor of a conference that considered shortcomings in postmarket surveillance of cardiovascular devices (O'Shea et al., 2004). (Other sponsors included FDA, the Agency for Healthcare Research and Quality, and the trade group AdvaMed.)

Joint Commission

The Joint Commission on the Accreditation of Healthcare Organizations is best known for its long history of accrediting and setting detailed standards for hospitals and other health care organizations. Many of these standards involve the safe use of medical equipment.

As part of its standards, the Joint Commission has also identified a set of sentinel events that are subject to reporting and review. Sentinel events, which are incidents that "signal the need for immediate investigation and response," are defined as unexpected occurrences that involve "death or serious physical or psychological injury, or the risk thereof" and do not result from the patient's medical condition (JCAHO, 2005a, unpaged).

Thus, they include both serious adverse events and close calls. Accredited health care organizations are expected to have internal policies and procedures for analyzing and responding to sentinel events, including the application of a root-cause analysis.

Certain sentinel events are reviewable by the Joint Commission when voluntarily reported by hospitals or when otherwise identified (e.g., through a newspaper story or a patient report). One type of reviewable event is a perinatal death that is not related to a congenital condition in an infant with a birth weight greater than 2,500 grams. A root-cause analysis of the 84 such events reported between 1995 and 2004 found that the most frequent contributing factor was communication problems (JCAHO, 2004).

Between 1995 and the end of 2004, the Joint Commission reviewed nearly 3,000 sentinel events (JCAHO, 2005b). The organization continues to be concerned about a low level of voluntary reporting, which limits the utility of the effort as a source of information about the nature and causes of events. One early review of the Joint Commission program suggested that if it had had the same yield as New York's event reporting program, it would have received as many as 21 times the reports it actually did during the period reviewed (Wald and Shojania, 2001a).

ECRI

The most comprehensive private program of adverse event reporting and analysis related to medical devices is maintained by ECRI, a private nonprofit health services research and technology assessment organization. Among other activities related to patient safety, ECRI gathers and investigates reports of incidents involving medical devices from health care providers, patients, and manufacturers around the world. It provides investigative and consulting services to health care providers, governmental health agencies, and other organizations. Each year the organization receives more than 1,000 high-quality reports of medical device adverse events and publishes scores of original hazard reports on specific device models as well as problems generic to classes of medical devices. In 1973, ECRI's problem reporting program served as a model for the newly emerging FDA Device Experience Network.

ECRI's monthly journal, *Health Devices*, includes independent medical device evaluations (e.g., recent evaluations of infusion pumps [ECRI, 2004c]) and reports on device safety. Another publication, *Health Devices Alerts*, provides weekly reports on medical device hazard and recall information, product safety alerts, reported problems and recommended responses, and published research on medical devices. In addition to the reports on circumcision clamps cited earlier, a number of ECRI reports

have dealt with safety issues related to devices used with children, including incubators, cribs, ventilators, and automated external defibrillators.

Under contract to FDA, the organization developed the education and training materials for recognition, investigation, and root-cause analysis of medical device adverse events for the pilot MedSun program. ECRI also assists in the analysis of the MedSun problem reports. In addition, ECRI has a contract with FDA to help harmonize FDA's medical device product codes with the Global Medical Device Nomenclature (GMDN). It recently drafted a white paper for FDA on the automatic identification of medical devices.

CONCLUSIONS AND RECOMMENDATIONS

One theme of this report is that an effective regulatory program for evaluating and monitoring the safety of medical devices in general is a necessary foundation for efforts to safeguard children in particular. Thus, steps to improve FDA's programs for the reporting of adverse device events overall should benefit children as well as adults. To promote more focused attention to pediatric issues, Chapter 7 includes a recommendation (7.1) that FDA identify a focal point of responsibility for pediatric issues within the Center for Devices and Radiological Health to evaluate the adequacy of the Center's use of pediatric expertise and its attention to pediatric issues in all aspects of its work to promote medical device safety.

Another theme of this report is that medical device safety is a shared responsibility. The recommendations below start with FDA but extend to include manufacturers, health professionals, user facilities, and patients and families. Chapter 7 extends this discussion.

Within FDA, adverse event reporting and improvement should be understood in the entire context of the agency's activities to protect patients and promote medical device safety from the early stages of device development through the end of a device's useful life. These activities include guidance for developers of devices, premarket evaluations, systematic postmarket clinical studies of selected devices, public health notifications and additional information for users of devices, quality system inspections of manufacturers, and other strategies. The FDA program itself should be seen as part of a more expansive system of public and private programs and actions to safeguard patients and improve health outcomes.

FDA Adverse Event Reporting

As part of a larger system of postmarket surveillance and device safety regulation, a passive or spontaneous program of reporting has a role to play in detecting unexpected device problems (including problems with the use

of a device) and increasing understanding of certain already recognized problems. Adverse event reports may provide the first signal that a problem exists with a device or its use or both. Adverse event reporting is particularly important for medical devices in pediatric use because events involving children are often unusual, are sometimes extreme, and identify problems in a patient population that often has not been studied before a device is marketed.

Certainly, this report and many other analyses of spontaneous event reporting programs across diverse realms make clear that such programs have significant limitations. These limitations include underreporting, poor-quality reports, delayed reports, reports of problems not associated with a device (i.e., false-positive reports), and lack of information needed to compute and compare rates of events. Efforts to investigate a worrisome event report may be frustrated by distance in time and place from the event, with consequent loss of critical information about the circumstances surrounding the event and unavailability of the suspect device or devices for analysis. The adequacy of FDA resources for event analysis is also a concern.

Initiatives to increase the spontaneous reporting of adverse events present a dilemma. On the one hand, there is general agreement that serious events are underreported; on the other hand, there is concern that increased reporting would likely bring an increase in reporting not only of serious events but also of "noise," that is, reports that are of no real interest, that are so poorly prepared as to be useless, or that do not even involve device problems or adverse events. Such reports waste the resources of all involved.

Nonetheless, the committee believes it is important for FDA to sustain and improve its adverse event reporting program and demonstrate its value. One objective should be to improve links between the reporting program and various FDA databases, including the databases for device recalls, enforcement, and public health notifications. For example, someone reporting or considering reporting a device problem through the online MedWatch option should be able to link easily and clearly to public health or recall notifications related to the device in question.

FDA should also consider how to encourage reporters to identify when an event involves a child. In some cases, a facility reporter or a manufacturer will know that an incident involved a child without having the child's exact age. It would be desirable to give such reporters an explicit opportunity to mark whether an event involved a child (age unknown). (The committee recognizes that changing the adverse event reporting form is a major, complicated undertaking, but encourages that this change be evaluated the next time that FDA or Congress considers revisions.)

Recommendation 4.1: FDA should collaborate with industry, health care professionals and organizations, and parent and patient advocates to

- **focus more attention on adverse device events, including events involving children;**
- **promote linkages between adverse event reporting systems, various FDA databases, and other safety programs;**
- **update product labeling, patient information, and other communications to promptly reflect safety-related findings from analyses of adverse event reports; and**
- **issue yearly reports on results from adverse event analyses, including findings involving children.**

Recommendation 4.2: FDA should continue educational and communication programs to promote recognition and useful reporting of serious adverse device events and device problems by hospitals and other user facilities. Such encouragement should continue whether or not requirements for mandatory reporting by user facilities are eventually eliminated with the effective implementation of the MedSun program. Reporting by user facilities of events possibly related to devices should continue to include deaths, serious injuries, and device malfunctions.

In addition, as suggested earlier in this chapter, FDA should continue its efforts to educate providers about HIPAA and the legality and value of providing information to support postmarket surveillance. Such information includes not only adverse event reports but also data for required postmarket studies as discussed in Chapter 6.

The legislation creating pilot MedSun program provided that mandatory reporting requirements for user facilities should end when the program is fully implemented. Before that happens, the evaluation of the program should consider MedSun's performance both as an active surveillance system (e.g., responding to FDA inquiries, conducting special studies) and as a spontaneous reporting system for detecting serious unexpected device events. Given that many manufacturer investigations and reports of adverse events start with reports from user facilities, one question is whether it is prudent to eliminate mandatory reporting for these facilities, even if the limitations of such reporting are recognized and facilities are not sanctioned for failure to report. It would be unfortunate if user facilities felt even less responsibility to report serious events and deaths in the future.

The careful evaluation of the pilot MedSun program will be critical. Although a formal evaluation is premature given that the pilot program is not fully implemented, FDA should be putting in place the data collection resources it will need for the evaluation. The evaluation should include an assessment of the extent to which reporting by non-MedSun facilities generates signals of significant device problems that are not reported by MedSun

facilities (because they did not experience them or because they either did not detect them or did not report them). It is important for FDA to audit participant performance, including the periods when initial participants rotate out of the program and new facilities replace them.

Recommendation 4.3: FDA's plan for evaluating MedSun's performance as a replacement for and improvement on mandatory user facility reporting should include, among other elements:

- **assessment of ongoing program and participant facility success in educating facility personnel about identifying, evaluating, and reporting adverse device events and improving the quality, timeliness, and usefulness of event reports;**
- **determination of the extent to which the sample of MedSun participating hospitals—including children's hospitals—represents the relevant range of facility characteristics and experiences, including representation of both academic medical centers and community hospitals and sufficient representation of facilities with device-oriented specialties and procedures;**
- **comparison with the mandatory user facility reporting system, including the extent to which either program produced reports for FDA or manufacturers of emerging hazards, important close calls, or other significant events (including those involving children) that were missed or delayed by the other; and**
- **evaluation of the active surveillance components of the program in reducing harm to patients, promoting constructive communication between facilities and FDA, and improving timely knowledge of the nature and extent of selected device problems, including errors in the use and design of devices.**

Prior to formal evaluation of MedSun, the committee encourages FDA efforts to extend to other institutions the lessons the agency and participants learn as they implement the program. For example, after their value has been assessed and revisions considered, the training materials developed for MedSun participants could be made more widely available. It is reasonable to provide MedSun participants with incentives to participate, but the written materials used in the program are only a small part of these incentives. Likewise, FDA should consider whether the information in the newsletter provided for MedSun participants could be used, at least in part, as a communication tool to inform interested parties in other facilities and encourage timely, complete, and appropriate reporting of adverse device events and other device problems to manufacturers and FDA. Despite the agency's claim

that its discontinued user facility newsletter had served its purpose, the problems of facility underreporting and poor-quality reporting remain significant.

The committee commends FDA for the oversampling of children's hospitals in the MedSun program. The MedSun participating children's hospitals should be considered not only as a particular resource for investigation of safety questions related to children but also as a resource or base for a broader set of device safety activities involving children's hospitals, CHCA, and NACHRI.

Recommendation 4.4: Within the pilot MedSun program, FDA and participating children's hospitals should serve as a resource for the broader involvement of children's hospitals in patient safety programs to identify, evaluate, respond to, or prevent problems with the use and design of medical devices. In addition, FDA should promote efforts to link or otherwise employ event reporting, device recall, safety notification, and other databases within and outside FDA to better assess and report on device safety issues involving children.

Information generated by MedSun could also prove more broadly useful. For example, it could be shared with academic clinicians and engineers to stimulate studies to identify device redesign or other strategies to prevent identified problems.

This chapter has noted the lack of a practical, precise coding scheme for medical devices that allows identification of specific models and brands of implants and other devices. Chapter 6 includes a recommendation (6.2) for the development and adoption of common device coding and other standards and approaches for capturing and linking use and outcomes data for medical devices.

Manufacturers

Sophisticated manufacturers recognize good adverse event reporting as a resource to help them learn about and correct problems with existing devices and identify areas for design refinement or product innovation. If adverse event reporting programs for devices are to improve device safety, manufacturers must receive timely and useful event reports, maintain sound procedures for evaluating these reports, and respond to identified problems on a timely basis. FDA regulations provide detailed direction on manufacturer responsibilities, and site inspections include a review of manufacturer compliance.

In addition to designing and redesigning devices to protect against unsafe use, promoting the safe use of devices is another important responsibility of device manufacturers. For some complex, high-risk implants and other devices, safe and effective use may require professionals to develop

new procedural and assessment skills. Some manufacturers have established mechanisms to develop and evaluate the competency of professionals to use such devices, and expectations for training and competency may be reflected in the labeling of the device. Training associated with such devices should cover the identification and reporting of adverse events.

Recommendation 4.5: When FDA mandates or agrees to device labeling that requires professionals to be trained in the safe and appropriate use of a medical device, the training should include information on the identification of adverse events, voluntary adverse event reporting under MedWatch, and user facility and manufacturer medical device reporting (MDR) requirements.

In addition, for complex devices that involve monitoring or operation by patients or families, manufacturers should provide directions about when and where to seek help, advice on reporting problems, and instructions, warnings, and troubleshooting guidelines that are understandable to nonprofessionals. Some manufacturers already have strong patient education and assistance programs. For certain home-use devices, FDA should consider requirements that manufacturers of certain devices (e.g., the orthodontic headgear mentioned earlier) affix labels stating that injuries related to the device can be reported to FDA.

FDA inspections of manufacturers should continue to include, as part of quality systems inspections, attention to complaint handling and event investigation and reporting. As discussed in Chapters 3 and 7, such inspections are occurring substantially less frequently than required by law.

Health Professionals and Professional Organizations

For many if not most medical devices, health care professionals who care for children occupy the critical intersection between device manufacturers and children and their families. They are well positioned to understand devices, evaluate their successes and failures with individual children, receive early warning of problems through professional networks, and determine what kinds of education health care workers—and patients or families—need to use devices safely. Significant complications with devices are often first reported at professional meetings without prior reporting to FDA, manufacturers, or other patient safety programs. Child health professionals are thus an essential but underdeveloped resource for identifying and reporting adverse device events. The challenge is how to better employ this resource to protect patients.

One difficulty is that pediatricians and other child health professionals are bombarded with advice, guidance, directives, and educational materials of all sorts. The likelihood that these incoming messages will change behav-

ior (or even be read) should certainly not be assumed, especially if financial and other pressures work in opposing directions. Nonetheless, incremental opportunities exist to improve recognition by child health professionals that medical device problems are reportable events, that reporting events has the potential to stimulate product and process improvements to benefit children, and that reevaluation rather than acceptance of certain common problems may be warranted.

For example, following direct mailings, continuing medical education, and other efforts to increase reporting by professionals to the Vaccine Adverse Event Reporting System (VAERS), the proportion of all vaccine adverse event reports that were attributed to health care professionals increased from 11 percent in 1991 to 35 percent in 2001 (Zhou et al., 2003). The committee recognizes that medical device reporting involves a vastly larger array and diversity of products, but FDA can collaborate with professional societies to set priorities for educational efforts. The agency can work with pediatric and other professional societies and journals, residency programs, and other resources to add messages about recognizing and reporting adverse device events to the messages that are already being disseminated about reducing health care errors and improving the quality of care for children.

In discussions with professional groups such as the American Academy of Pediatrics (AAP) and others, the committee found a general willingness of the groups to become more involved in efforts to promote the safe use of medical devices with children (AAP et al., 2004b; ACC, 2004; ATS, 2004a). These efforts encompass both the reporting of adverse events and the expanded use of registries as well as other means of developing better information about the short- and long-term outcomes of medical device use.

Recommendation 4.6: Medical, surgical, and other organizations or societies that include health professionals who care for children should

- **establish working groups to evaluate problems as well as benefits in the pediatric use of devices of particular importance to their practice;**
- **collaborate with existing public and private patient safety initiatives to add or expand attention to safe and appropriate use of medical devices with children;**
- **establish standards for professional education and competency in the use of these devices; and**
- **include as professional competencies the identification and appropriate reporting of device problems and the successful communication with patients and families about how to prevent, recognize, and respond to device problems.**

Information from adverse event and case reports as well as systematic clinical studies and registry-based research will help provide a stronger evidence base for pediatric practice guidelines and standards of competency. These guidelines and standards should, in turn, reduce the unsafe and unnecessary use of devices.

Hospital and Other Device Safety Programs

Hospital and other patient safety programs that now focus almost exclusively on errors or problems involving other medical products and services can extend their reach. For example, for devices used with children, possible targets for such programs include certain types of common workarounds that have not been assessed adequately to determine the extent to which they constitute reactions to device problems, pose risks of their own, or warrant reconsideration of the way devices are used or designed.

One objective of the MedSun program is to encourage more coherence in user facility device safety programs. Children's and other hospitals generally lack the kind of obvious focal point for medical device safety that pharmacists provide for drugs. Clinical engineering units, risk management departments, an array of clinical units, quality assurance programs, materials management divisions, purchasing departments, and other units share a fragmented and incomplete accountability for device safety.

Recommendation 4.7: Children's hospitals and other user facilities should establish a focal point of responsibility for medical device safety. Tasks include reviewing and monitoring the adequacy of institutional programs in areas such as tracking of safety alerts and recalls, responding to safety alerts and recalls, training in adverse event evaluation and reporting, and factoring safety data or evaluations into device purchase decisions.

FDA should also charge its home health committee with investigating the role of home health agencies and vendors that supply home medical equipment in reporting adverse events and examining what might be done to support these providers. It is important that these organizations focus on identifying and resolving problems, but it is also important that serious problems be reported to manufacturers and FDA. A better understanding of problems with devices used in the home may promote refinements in the design of such devices, changes in the selection and monitoring of devices for home use, and improved information and training for patients and families.

Resources for Patients and Families

Given the continued movement of complex care into the home, FDA should seek more creative ways to publicize its device safety activities and resources to patients and families, particularly families caring at home for children who rely on complex, life-sustaining medical devices. The CDRH checklist on medical devices for home use is a good model that should be more widely disseminated, including by professional and provider groups such as AAP and NACHRI.

Adverse event reporting will hardly be a first priority for families who confront a problem with a device. Troubleshooting and getting assistance from health care professionals, manufacturers, and home care agencies or vendors will take precedence, especially if the problem involves a life-supporting device. Nonetheless, some families may appreciate the opportunity to report their experiences with device problems further, for example, by sharing what happened and what was learned with other families through various kinds of family and patient support groups.

Some families may learn that they can report problems to FDA. The agency sensibly advises consumers who wish to report adverse events to seek the assistance of their physicians, who can provide clinical and technical details that may be important in understanding and describing the nature of the problem. Some patients and families, however, may wish to report directly to FDA without involving a physician. They may, for example, worry about alienating a physician they depend on by complaining about a device that the physician prescribed. They may also feel that a physician has ignored or dismissed their observations about a problem because their description of an event or problem was not technically sophisticated. Such dismissal risks overlooking real problems observed by those who are with the patient for extended periods.

Although FDA may have qualms about the quality and utility of the information received from patients and families, it still should offer consumers easier opportunities to report. As discussed earlier, the consumer who wishes to report a problem through the agency's MedWatch program now faces instructions that are not written with the layperson in mind.

FDA should enlist its home health committee and others in advising on the creation of a simpler event reporting form in lay language for consumer reporting of events. (Again, the committee recognizes that changes in Form 3500 or 3500A involve a lengthy process.) The agency's online reporting option could also be modified to provide additional explanations and assistance aimed specifically at lay users. Ideally, the online reporting option would also be designed to provide some feedback to reporters, for example, by directing consumers to additional resources such as advice on discussing concerns with a manufacturer or vendor and instructions about returning a

device (with problem documentation) to a manufacturer or vendor. It could provide links to reports on safety problems with a device that is the subject of a consumer's report. The committee recognizes that it is not feasible to provide individualized feedback for each consumer report, but information technologies have the potential to allow more than a computerized thank you or acknowledgment of a report.

Recommendation 4.8: FDA should continue to improve and expand its medical device safety resources for patients and families and its focus on devices used in the home and community by

- **working with patient, family, and consumer organizations, providers, and industry to make it easier for patients or their families to report device problems to manufacturers or FDA and to learn about resources to support the safe use of medical devices;**
- **making online reporting and information resources more accessible by using language and directions appropriate for lay users; and**
- **enlisting hospitals, home care agencies and vendors, and other professional and provider groups to promote patient and family understanding of how to use devices safely, when and how to seek help, and when and how to report problems.**

The recommendations above cover many areas for improvement in the agency's adverse event reporting program for medical devices. At the same time, Congress and FDA deserve credit for past and continuing efforts to improve the program. These efforts include, for example, creating an online reporting option, developing computerized aids to screen reports and identify problems, creating a more active surveillance initiative in the pilot MedSun program, and using adverse event reports to inform the agency's human factors research program.

In addition to continuing efforts to improve the existing program and fully implement the MedSun program, FDA is investigating additional forward-looking or prospective strategies based on automated patient information systems that would not only improve the detection and investigation of adverse events but also identify device hazards or hazardous practices before they cause harm to patients. The agency recognizes that this strategy requires improved means of identifying medical devices for purposes of analyzing and responding to adverse event reports. In particular, codes for use in the medical record should allow identification of both the manufacturer and model of a device rather than, as now, a general category of device (e.g., apnea monitor).

The next chapter of this report shifts attention to a different dimension of postmarket surveillance of medical devices. It examines the monitoring by FDA of postmarket studies required by FDA.

5

Monitoring of Postmarket Study Commitments Involving Medical Devices

"We have not done a great job [in following through on post-market studies]. . . . There is basically very little confidence among our premarket reviewers in saying, 'We can study this and answer these questions post-market.' In many cases, those questions never get answered."

Daniel Schultz, Director, Center for Devices and Radiological Health (quoted in Dickinson, 2004a, unpaged)

The quote above reveals that the U.S. Food and Drug Administration (FDA) recognizes that it has not done well in monitoring the status and fulfillment of studies that it has required in connection with the premarket approval of medical devices or subsequently. To the extent that significant questions related to device safety have been asked and then neglected by the agency, the result may be avoidable harm to patients and their families and a breach of public trust. As this report was being completed, the agency announced plans to create a monitoring system and shift responsibility for monitoring to the unit within the Center for Devices and Radiological Health (CDRH) that is responsible for postmarket surveillance.

As described in Chapter 3, FDA may require studies of medical devices after they have been approved. Most such studies are ordered as a condition for approving a premarket approval application (PMA) or a Humanitarian Device Exemption (HDE). In addition to these "condition-of-approval" studies, section 522 of the Federal Food, Drug, and Cosmetic Act (P.L. 75–717) allows FDA to direct studies or other information collection for certain high-risk, implanted, or life-sustaining Class II or III devices after their approval or clearance. (At least once, as described later in this chapter, FDA has required both a condition-of-approval study and a 522 study for a Class III device.) Because both condition-of-approval studies and Section 522 Postmarket Surveillance studies are necessarily conducted after mar-

keting of a device is permitted, this report refers to both types of studies collectively as postmarket study commitments.

The statutory provisions for postmarket studies reflect Congressional awareness that the data and assessments associated with the approval or clearance of a complex medical device may leave meaningful unanswered questions about uncommon adverse events, effects in groups not studied (e.g., children), and long-term effects. To the extent that FDA encourages and accepts smaller, faster, and otherwise more limited studies to promote earlier consideration of a device for approval and reduce burdens on sponsors, more questions may remain for the postmarket period. Thus, attention to the specification and monitoring of postmarket study commitments becomes more critical.

This chapter examines FDA's monitoring of the status and fulfillment of commitments for postmarket studies of medical devices. It starts by providing some background on concerns about the monitoring of postmarket studies as they initially arose with pharmaceutical products. It also describes growing interest in public access to information about findings from such studies through some kind of clinical trials registry. The chapter then reviews the FDA's monitoring of postmarket study commitments for devices. The final section presents the committee's conclusions and recommendations about monitoring and public information. The discussion of trade secrets and confidentiality in Chapter 3 provides important additional context.

This chapter does not report on studies that sponsors initiate voluntarily. Sponsors often undertake such studies to support expansions in the labeling of a device to cover new uses or populations. Voluntary studies may also be negotiated between sponsors and FDA at the time a device is approved, possibly as an alternative to a required study. In addition, sponsors may initiate further studies to provide information sought by Medicare and private health plans to guide coverage decisions. Recent years have seen Medicare and some other health insurers become interested in supporting clinical trials of some innovative products or procedures as a way of obtaining better data for clinical and coverage decision making (see, e.g., IOM, 2000a).[1]

[1]In 2000, the President issued an executive memorandum that, in essence, directed the Medicare program to pay the routine costs of patient care and the costs of treating medical complications associated with participation in clinical trials (CMS, no date). The Centers for Medicare and Medicaid Services (CMS) recently announced related initiatives, including that Medicare would cover positron emission tomography (PET) for some Medicare beneficiaries who are at risk for Alzheimer's disease and who enroll in a clinical trial approved by Medicare (CMS, 2004).

BACKGROUND

Although the regulation of devices differs from the regulation of drugs in some respects, the monitoring of study commitments is essentially a generic task. Thus, a brief review of the evolution of FDA monitoring of postmarket study commitments for drugs will provide useful context for the consideration of such monitoring for studies involving medical devices.

FDA Shortfalls in Monitoring Postmarket Drug Studies

In 1992, new regulations provided FDA with authority to grant accelerated approval for drugs to treat serious or life-threatening conditions based on clinical trial data about certain surrogate endpoints or clinical endpoints other than survival or irreversible morbidity (21 CFR 314.510; FDA, 1992).[2] These regulations remain in place. Should uncertainty exist about the relationship of surrogate endpoints to clinical benefits or observed clinical benefits to ultimate outcome, the regulations specify that applicants are to continue research to verify clinical benefit, usually by continuing studies that are already under way.[3] In addition, applicants may also commit to conduct postmarket studies after a drug has been approved. If a mandatory postmarket study is not completed or does not confirm the expected benefit, FDA may order the drug withdrawn from the market (21 CFR 314.81(d) and 21 CFR 314.530).

In 1996, the Office of Inspector General (OIG) of the U.S. Department of Health and Human Services (DHHS) undertook a study of the effectiveness of FDA monitoring of postmarket studies for prescription drugs (OIG, 1996). It found that the Center for Drug Evaluation and Research (CDER) had established a listing of study commitments associated with original drug applications and a list of drugs for which study commitments had been met (or determined to be infeasible or unnecessary). Key agency staff (e.g., CDER division directors and the reviewers who propose specific condition-of-approval studies) were not, however, aware of the list, and the list was not public. This limited the list's potential value in identifying study commitments that had not been met.

---

[2]The regulations specified that the surrogate endpoints should be "reasonably likely, based on epidemiologic, therapeutic, pathophysiologic, or other evidence, to predict clinical benefit" (21 CFR 314.510; FDA, 1992, p. 58944).

[3]For drugs under review that are subject to requirements for studies in pediatric populations under the Pediatric Research Equity Act of 2003 (P.L. 108–155), FDA allows such studies to be deferred until after a drug is approved for use with adults. Deferred studies are considered postmarket studies and if not completed, FDA may declare the drug to be misbranded. Studies may be waived under certain conditions (e.g., if they cannot be practically or ethically conducted). FDA can also require studies of already marketed drugs that lack adequate pediatric labeling if voluntary efforts to secure the necessary clinical studies have failed.

The OIG report concluded that FDA—specifically CDER—lacked effective methods to track study commitments and was too dependent on the memory of individual staff members. Although the report credited the agency with taking steps to improve its procedures and systems, it also found that the agency had no formal standards to establish whether commitments for postmarket studies of prescription drugs were met. The time taken by the agency to review submitted reports for postmarket studies and determine whether they were acceptable varied from a few days to several years.

In its report, OIG recommended that FDA should establish accountability for monitoring postmarket study commitments for drugs and develop standards, procedures, or guidelines for doing so. The report recognized that the agency's limited resources had been subject to further pressure by legislative provisions for accelerated review of premarket applications for drugs.

Action to Monitor Postmarket Study Commitments for Drugs

In the FDA Modernization Act of 1997 (P.L. 105–115), Congress added new responsibilities for both FDA and companies related to postmarket study commitments for drugs (21 USC 356(b)). It required sponsors who had postmarket study commitments to report annually to FDA on their progress in fulfilling the commitments.

In addition, for drugs and biologics, the 1997 legislation required FDA to report annually in the *Federal Register* on sponsor performance and to submit a report on postmarket studies to Congress in 2001. The legislation provided further that FDA was to treat information related to the studies as public information "to the extent that the information is necessary to identify the sponsor, establish the status of the study, and find the reasons, if any, for failure to complete the study."

Subsequently, in the Public Health Security and Bioterrorism Preparedness and Response Act of 2002 (P.L. 107–188), Congress provided that FDA's website include information about unfulfilled drug study commitments (21 USC 356(b)). The legislation also allowed the agency to require the sponsor responsible for such a study to inform relevant practitioners about unfulfilled commitments and any questions of clinical benefit or safety that continue unanswered as a result. Congress did not otherwise provide for the public availability of information about study findings, and the database created by FDA does not include such information.

In March 2002, FDA presented the required report to Congress on studies involving drugs and biologics (FDA, 2002p). It also published the requisite annual reports in the *Federal Register* in 2003, 2004, and 2005. In the 2005 report, FDA stated that annual status reports were due but not submitted for 16 percent of the open study commitments associated with

new drug approvals (FDA, 2005j). Of the studies concluded from October 1, 2003, through September 30, 2004, 27 percent were described as concluded because they were judged to be no longer needed or not feasible. In contrast, the corresponding figure for the previous 12 month period was 6 percent (FDA, 2004x). Of the 1,191 drug studies described as having open commitments, 68 percent were labeled as "pending," by which the agency means that the study has not been started but is not considered delayed (i.e., behind its original schedule) (FDA, 2005j). This figure has attracted criticism (see, e.g., Nature Publishing Group, 2005).

On the agency's study commitments website, the entries for study commitments (which are organized by sponsor) provide brief details about the purpose of the study. They identify study commitments by status, for example, pending, ongoing, delayed, terminated, submitted, fulfilled, or released (i.e., sponsor released from study commitment). The agency has not, to date, required that sponsors to inform practitioners about unfulfilled study commitments and any related unanswered questions (personal communication, Beth Duvall-Miller, Project Management Officer, Center for Drug Evaluation and Research, October 22, 2004).

Information about study status is removed one year after a sponsor fulfills a study commitment or is released from that commitment. Thus, those outside FDA cannot use the database to obtain information about the fate of these past study commitments.

Entries in the online database identify whether studies resulted from accelerated approval or requirements of the Pediatric Research Equity Act of 2003 (P.L. 108–155). As of January 31, 2005, 78 drug applications with such pediatric study commitments were listed, including those completed within the preceding year. Of these, 66 were described as pending (i.e., not started).

The drug study database does not allow a search for postmarket pediatric studies that were *not* required under P.L. 108–155. Because no search capacity exists for these study commitments, a study-by-study review of database entries is required to identify them. Also, because information about study findings is not included in the database or made accessible by a link to other information sources, the database does not contribute to the greater availability of public information about the safe and effective use of drugs with children.

Proposals for a Registry of Clinical Trials

The FDA study commitments database for drugs is not intended to serve as a registry of drug studies for the purposes of making more comprehensive information available about what clinical trials have been initiated and completed and with what aims and results. A number of groups have proposed some form of clinical trials registry in response to concerns about commer-

cial, professional, journalistic, and other biases that favor reporting of positive findings and discourage reporting of unfavorable or inconclusive study results. This disparity in reporting deprives clinicians and the public of balanced and potentially critical information (see, e.g., AMA, 2004a,b; DeAngelis et al., 2004; Steinbrook, 2004). A related concern is that when the details of original study designs or protocols are not public, investigators or sponsors may be encouraged to report incidental and misleading positive findings from analyses that were not planned in the study protocol, while ignoring the unfavorable results of analyses of the original study hypotheses. One consequence is that meta-analyses, review articles, editorials and other commentaries, and prescribing information may be inaccurate or misleading because the authors lack adequate information about the original study questions and study design (Steinbrook, 2004; see also Chalmers, 1977; IOM, 2000a, 2003; Dickersin and Rennie, 2003; Couzin, 2004).

An additional, ethical argument for greater public access to clinical trials information derives from the obligations to research participants of research sponsors (and those who review and approve research). "If the knowledge gained in a trial is never communicated to others, then their [research participants'] contribution is unrealized and the covenant between researcher and patient [research participant], indeed between ethical review boards and patients, is broken" (Dickerson and Rennie, 2003, p. 517). In 2003, an IOM report on the responsible conduct of clinical research stated that the "creation of a comprehensive clinical trails database that is soundly structured for public use would ensure that information . . . would be available to contribute to generalizeable knowledge regardless of whether [the] results are viewed as positive or negative by investigators, sponsors, or publishers" (IOM, 2003, p. 204).

Proposals for clinical trial registries vary in comprehensiveness, quality, and force, differing, for example, on what types of interventions and study designs would be included and whether registration would be mandatory or entirely voluntary.[4] In general, the more comprehensive registry propos-

[4]Under provisions of the FDA Modernization Act, FDA worked with the National Institutes of Health (NIH) to create a clinical trials databank for pharmaceutical products only (FDA, 2002h). At the top of the website for database is the phrase "linking patients to medical research," which captures the primary intent of this databank (http://www.clinicaltrials.gov/). Listings provide information about a trial's purpose, locations, and eligible participants, and they include phone numbers to call for more details. The 1997 legislation directed FDA to report on the feasibility of including device clinical trials in the database. That report, which was submitted in November 1999, recommended that no action be taken to include devices until experience with registration of pharmaceutical trials was evaluated (FDA, 1999a). The report also recommended that inclusion of device trials be limited to life-threatening or serious conditions for which no alternative therapies exist.

als—including those offered by the American Medical Association (AMA) and the International Committee of Medical Journal Editors—would require research sponsors to provide information about the original study protocol (e.g., the original study hypothesis, study populations, and planned analyses as approved by an Institutional Review Board [IRB] or equivalent body). They would also require sponsors to publish or post key findings in some form once a study was completed, although critical questions arise about the listing of information that has not been through some sort of peer review or vetting process. Proposed incentives or sanctions include requiring registration as a condition for Institutional Review Board approval of a research protocol (AMA) or refusal by major medical journals to publish articles based on trials that had not been prospectively registered (journal editors). Action by Congress might be required.

Some proposals cover only drugs (e.g., that of the Pharmaceutical Research and Manufacturers Association, see http://www.clinicalstudyresults.org). The journal editors' proposal would include only prospective clinical trials with intervention and comparison groups. They thus would exclude many single-arm, so-called pivotal clinical studies that are initiated and relied on to support initial FDA approval of high-risk medical devices or additional indications for their use. They likewise would exclude many of the postmarket studies discussed in this chapter. Others have called for more inclusive criteria (see, e.g., Rennie, 2004).

Most proposals appear to envision that the registration of a trial would be public from the outset. In commenting on proposals to include device trials in an existing trials databank, the device industry has argued that an early and detailed listing of trial information could reveal trade secrets and other confidential information and thereby damage the competitive advantage associated with being the first company to introduce an approved device in an industry that derives far less protection from patents than the pharmaceutical industry (see FDA, 1999a).[5] Respecting sponsors' concerns about confidentiality, the goal of open information about results of trials covered by FDA regulations might still be served by allowing information about studies to remain confidential for a period of time prior to completion of a study (unless the details are already in the public domain, e.g., through release of information by sponsors).

Many important questions remain about how to construct a trials reg-

[5]Other industry concerns are that requirements for registering trials and associated responsibilities (e.g., responding to inquiries from people interested in enrolling in trials or simply wanting more information) would impose particular burdens on small companies, especially if requirements extended beyond studies involving serious or life-threatening conditions for which no alternative therapy existed.

istry that will serve the public interest. One of the most important involves criteria for registration and publication that will avoid the publicizing of studies that are badly designed, poorly executed, or inappropriately analyzed or that are not intended to build scientific and clinical knowledge. The discussion below returns to this issue as it relates to monitoring and reporting required postmarket device studies.

MONITORING OF POSTMARKET STUDY COMMITMENTS FOR MEDICAL DEVICES

Congress has not established monitoring requirements for required postmarket device studies that are equivalent to those created for drug studies. Section 104 of the Medical Device User Fee and Modernization Act of 2002 (P.L. 107–250), however, requires a report from the agency by 2007 on the effect of medical device user fees on FDA's ability to conduct postmarket surveillance, the extent to which device companies comply with postmarket surveillance requirements (including postmarket study commitments), any improvements needed for adequate postmarket surveillance, and the amount of funds needed to do so. The agency is in the early stages of developing this report.

The committee's investigation of the current status of FDA monitoring of postmarket study commitments of devices (also provided for in P.L. 107–250) yielded little information about the objectives for required studies or the extent to which companies have met their commitments. Information available on the website of CDRH, which was helpful in much of the committee's work, was minimally useful for this task. Currently, no current overall compilation or summary of information on study commitments or their status is available from CDRH.

In an effort to learn more about the monitoring of postmarket study commitments, the committee sent a letter to CDRH. The letter included questions about condition-of-approval studies (for devices with a PMA), Section 522 Postmarket Surveillance studies, and any postmarket studies associated with the clearance of a 510(k) device.

Studies Required at the Time of Device Approval

CDRH, in its letter of response, referred to an internal database that contains information about PMA approvals that included requirements for condition-of-approval studies (Tillman and Gardner, 2004). As described in the letter, the database is not searchable and is limited to information in the approval letter. It thus does not include details about study focus and design that are determined subsequently or nor does it incorporate information about study status or results. It also is not public.

The CDRH letter stated that the agency is updating its information technology system and reviewing how it communicates requirements for the studies. It noted that the agency expects to create a searchable database that includes more information about condition-of-approval studies. Separate information from FDA indicated that the great majority of postmarket studies involve clinical investigations, but a few specify additional bench or animal studies (personal communication, Thomas P. Gross, M.D., Director, Division of Postmarket Surveillance, CDRH, November 9, 2004).

Although FDA cannot require studies as a condition for clearing a device under 510(k) procedures, it can encourage voluntary studies as part of discussions with sponsors related to clearance decisions. (Subsequent to clearance, the agency can order a Section 522 Postmarket Surveillance study.) Given that no comprehensive information is available on required postmarket studies, it is not surprising that such information is likewise not available on these kinds of voluntary studies.

As this study was nearing completion, FDA released an internal two-year-old report on the status of conditions-of-approval study commitments (after the *New York Times* filed a request for it under the Freedom of Information Act) (Meier, 2005). The report, which was essentially completed in 2003, examined the period from January 1, 1998, through December 31, 2000. It found that 45 (35 percent) of the 127 PMAs approved during the period examined included provisions for a postmarket study (Brown et al., 2005). For 26 of these, the report authors could find no mention of the studies in the manufacturer's annual reports (which are supposed to include such information). After additional data collection, including a survey of the lead reviewers for the approval applications, the authors found information on 16 of the unmentioned studies but could find nothing for 8. For 11 studies for which results were due (or past due), the agency had not received results for 6. The report provided no details about the topics of the required studies.

Subsequently, AdvaMed, a trade association representing device manufacturers, sent a letter to the Director of CDRH that reported the results of a survey of its members about the status of the 45 postmarket study commitments that were mentioned in the CDRH report (Secunda, 2005). The letter stated that 12 of its members were responsible for 22 of those 45 study commitments. These companies reported that 16 of the 22 studies were completed on time (as the time table was understood by the companies), that 2 were completed within a year of the expected date, and that 2 studies were ongoing. One study had been cancelled because the company withdrew the indication for which the study was requested, and the start of another study was being delayed until the product was widely enough distributed to generate a sufficient number of study subjects. The letter did not discuss whether the companies had appropriately reported on the stud-

ies in their annual reports. The committee considers the AdvaMed report encouraging for the studies it covered. It does not affect the committee's judgment that the agency must have an effective system for monitoring and reporting of the status of postmarket device studies.

In an effort to learn more about study commitments, committee staff read individual, online approval letters for the period from January 1, 2001, through December 31, 2004. Of the 168 letters read, 74 had some provision for postmarket study or information collection. As discussed in Chapter 6, some provisions involved pediatric use of a device. The committee could not review most approvals of PMA supplements (which may include study provisions or approve study protocols) because few are available online. The committee also identified postmarket study commitments in the online letters of approval for humanitarian device exemptions. Among six such devices explicitly approved for use with children since December 1997, one—for a left ventricular assist device—was subject to requirements for further study (H030003, FDA, 2004a).

The committee did not attempt to determine the specific status of the study commitments it identified. (It expects that many, if not most, studies would not yet be completed and that the most recently ordered studies might not have started.) As described in Chapter 3, study protocols and findings are considered confidential unless the findings lead to a public health notification or similar action.

Taken together, the information available to the committee paints a disappointing picture of the agency's performance in monitoring study commitments for medical devices, particularly given the criticism directed at the agency in the 1996 OIG report on the monitoring of postmarket drug studies. Agency staff report that they are working to create a system to track what postmarket study commitments exist and where they stand in terms of progress toward completion (Tillman and Gardner, 2004). Committee recommendations appear at the end of this chapter.

In response to the committee's question about postmarket studies involving devices used with children or devices with possible pediatric as well as adult uses, the agency stated that it had not recorded such information in the past. Because the Medical Device User Fee and Modernization Act of 2002 provided that user fees for PMA applications and 510(k) notifications be waived for devices intended *solely* for pediatric use, the agency will be able in the future to identify those applications and any studies associated with those devices. Such applications, by definition, do not involve devices with possible pediatric applications that are approved or cleared based on studies with *adults*. Thus, this mechanism will not help identify studies related to pediatric use of these devices.

Studies Required After a Device Is Marketed

In response to committee questions about postmarket studies ordered by the agency after market approval or clearance of a medical device, the letter from CDRH stated that the agency had "an Oracle-based document tracking system for these studies that contains information about the [postmarket surveillance] order, the plan submitted by the manufacturer, and all subsequent submissions, including interim and final reports" (Tillman and Gardner, 2004, p. 3). The letter also reported that CDRH has, in recent years, required only two Section 522 Postmarket Surveillance studies.[6] The progress of the plans for the two current studies is being monitored by an interdisciplinary review team, and "limited experience" indicates "that manufacturers are honoring these commitments" but "[n]either of the studies has yet reached the expected plan completion date" (Tillman and Gardner, 2004, p. 5).

Of the two Section 522 Postmarket Surveillance studies identified by FDA, one involves a device used in fever reduction that was cleared for marketing on August 1, 2003 (K014241, FDA, 2003). In May 2004, FDA required further study of a larger number of patients than were initially studied. The objective was to obtain more information about the mortality of patients treated with the device (in accord with the labeled indications for use) compared to patients receiving standard care. As the committee requested, FDA provided a copy of the letter.

The second Section 522 Postmarket Surveillance study involves an endovascular stent that was approved for marketing in 1999 (P990020, FDA, 1999). The original PMA approval letter included a provision for a 5-year study to assess the long-term safety and effectiveness of the device by continued evaluation of the subjects included in the study used to support the request for approval. The approval letter directed the company to analyze existing and newly collected patient data by gender to better identify the experience of women who received the device. Finally, recognizing the "learning curve" associated with a new, complex device, FDA required the company to continue its physician/team training program and evaluate its adequacy.

---

[6]As described in Chapter 3, Congress eliminated mandatory Postmarket Surveillance in 1997. In 1998, FDA issued a guidance document that described which surveillance requirements would continue and which would end (FDA, 1998i). For example, surveillance was to continue for saline breast implants but end for vascular grafts. In response to an inquiry about requirements that were left open in 1998, FDA responded that four studies of coronary stents remained open but should be closed out soon, and three studies of home-use prothrombin time test kits were still active (personal communication, Thomas P. Gross, M.D., Director, Division of Postmarket Surveillance, CDRH, November 16, 2004).

Then, in June 2001, FDA required the manufacturer to collect additional information to compare premarket and postmarket patient populations, examine types and rates of adverse events during premarket and postmarket periods, and determine compliance rates for patient follow-up (FDA, 2001m).[7] The committee requested and received a copy of the letter directing this study.

In December 2003, based on information received after market approval, FDA issued a public health notification for physicians with information about long-term mortality risks with the stent (Feigal, 2003). The data used for the public health notification were also used in a paper authored by FDA staff and an academic physician that was published on the website of the *Journal of Vascular Surgery*. Subsequently, as recounted in a July 2004 story in the *Wall Street Journal*, the article was removed from the website after objections and reference to legal action from the manufacturer of the device. The article was later withdrawn completely by FDA on grounds that the conclusions went beyond the public health notification (Mathews and Burton, 2004; see also Cronenwett and Seeger, 2004; Greenfield, 2004). According to the newspaper article and a statement by the surgery journal's editors (Cronenwett and Seeger, 2004), the company argued that the article relied on data that were confidential and proprietary and could not be used without company permission.[8] Like other recent incidents involving physician and public access to information from clinical studies involving antidepressant use with children and other drugs, this incident raises questions about the lack of public information about the results of postmarket commitment studies and the appropriate boundaries

[7]Two months earlier, in April 2001, FDA had issued a public health notification discussing problems with this device and one other (Feigal, 2001a). The notification stated that one device had been the subject of a voluntary production suspension and recall after the company revealed that it had failed to report many device malfunctions and adverse events (including severe vessel damage) and that an internal audit revealed problems with complaint handling, manufacturing quality systems, documentation procedures, and staff training. With respect to the other device, FDA described concerns about serious adverse events (e.g., aneurysm rupture, device migration) and reported that it was working with the manufacturer to collect additional data.

[8]The editors of the surgery journal expressed extreme disappointment that they were prevented from publishing an article with "data that we believe are important to readers" and that they viewed as "identical to the data in . . . other public documents" (Cronenwett and Seeger, 2004, p. 210). In a letter to the editors, the lead clinical investigator for the stent trials—who was highly critical of FDA's 2003 public health notification—called for publication of the article so that clinicians could judge whether it provided support for the agency's conclusions (Zarins and Bloch, 2004). The committee understands that the sponsor has expressed interest in an independent evaluation of the information it submitted to FDA but that it is still discussing the matter with FDA.

of trade secret and confidentiality requirements governing FDA (see, e.g., Ault, 2004; Avorn, 2004; Elliott, 2004; Richwine, 2004).

Under federal regulations, failure to comply with any conditions set upon the approval of a device constitutes grounds for withdrawing approval of the device (21 CFR 814.82(c)). As far as the committee is aware, this drastic penalty has never been applied for failure to complete a condition-of-approval study. For Section 522 Postmarket Surveillance studies, regulations provide that failure to conduct a required study would be a prohibited act such that the device would be misbranded under the agency's statute and that the agency could, among other penalties, impose civil money penalties (21 CFR 822.20). The committee is not aware of any situations when these penalties have been applied.

CONCLUSIONS AND RECOMMENDATIONS

A Monitoring System Should Be Established

Based on the information available to it, the committee must conclude that FDA has lacked effective procedures to monitor the fulfillment of postmarket study commitments as defined at the beginning of this chapter. The agency has lacked a basic, searchable listing of devices for which further studies were specified as a condition of their approval for marketing. Furthermore, it has not maintained any system for systematically monitoring the status of these study commitments based on periodic reports or updates from either its own staff or sponsors. The agency was able to identify the two postmarket surveillance studies (required under 21 CFR 822) that have been ordered in recent years. Overall, CDRH's arrangements for keeping track of postmarket study commitments for devices have been weaker than those criticized as inadequate in the Inspector General's 1996 report on monitoring of such commitments for approved drugs.

The committee recognizes that some requirements for certain postmarket studies may lack a compelling rationale, but that does not justify a failure to monitor study commitments. Manufacturers have—and should have—opportunities to make the case that a study is not feasible or will not produce useful results. FDA has released drug companies from study requirements in a number of instances, and the committee understands it has also done so for some device study commitments, although the committee has no information to judge the reasonableness of any such actions.

Given current deficiencies in monitoring, the committee has been pleased to learn that the agency is in the early stages of creating a system to identify and track postmarket study commitments and their progress toward completion. Responsibility for tracking studies is being reassigned within the CDRH to the unit responsible for postmarket surveillance. No

details were available about such matters as the timetable for rectifying current deficiencies or the allocation of adequate resources to track studies without undermining other postmarket surveillance activities.

As described earlier, FDA has until 2007 to prepare its required report to Congress on the extent to which companies comply with postmarket study commitments. The report to Congress should not be a one-time undertaking. Rather, it should be part of a continuing program of monitoring and public reporting of study commitments and their status.

The structure of the system for tracking and reporting study commitments for drugs and biologics provides a reasonable starting point for a CDRH monitoring program that includes a public information component. Some modifications are, however, desirable, including expanded search capabilities for the public database. Given the dearth of published information about device safety and effectiveness with children, a CDRH database should be searchable for any postmarket study commitments that involve pediatric populations or questions. (As noted above, the CDER public database cannot be automatically searched to identify all studies with pediatric questions but only those required under the Pediatric Research Equity Act of 2003.)

If FDA releases a sponsor from a study commitment, the monitoring database should record that with a meaningful explanation. Likewise, if a study is submitted but not accepted by FDA, that should be recorded with any follow-up actions described. Acceptance of a study should reflect the agency's determination that the study fulfills the commitment by being responsive to the questions originally posed for it. The committee believes that the monitoring system should also cover studies voluntarily agreed to by manufacturers as part of the discussions surrounding the approval or clearance of a device. Such studies may represent a particularly clear instance of FDA and manufacturer agreement on the importance of follow-up investigations.

Recommendation 5.1: Congress should require FDA to establish a system for monitoring and publicly reporting the status of postmarket study commitments involving medical devices. The system should also cover voluntary studies negotiated between FDA and manufacturers as part of the device approval or clearance process. The public database should, among other features, allow easy determination of the status of postmarket studies that involve questions about device use with children.

This recommendation reflects the committee's view that commitments for postmarket studies are a safeguard when FDA has important questions that are not answered by premarket studies. This safeguard is weakened when study commitments are not systematically tracked toward fulfillment.

The absence of a credible monitoring system also diminishes FDA's credibility as guardian of public health. Although FDA can act and is acting on its own to establish a monitoring system, Congress should make clear that key information about the status of studies (not merely their existence) should be public.

Findings from Postmarket Studies Involving Children Should Be More Accessible

The safeguard offered by postmarket studies is further weakened when useful findings generated by completed studies are not available to clinicians and patients or families. One limitation of the drug study monitoring database as a prototype is that it does not provide information on the disposition of study findings, for example, whether they resulted in a change in product labeling. In fact, that database does not provide any information about study findings—positive, negative, or inconclusive. The committee recognizes that Congress did not require that system to provide public access to information resulting from the required studies.

A study monitoring database for devices should, at a minimum, include a link to information about device labeling changes, safety alerts, and other decisions or actions that result from study findings. The database also should provide approved summaries of key findings or something equivalent. (Although recommendations about the creation of a clinical trials registry per se are beyond the scope of this committee, the issue of public availability of information about the safety and effectiveness of medical devices used with children is not.) If the results of a postmarket pediatric study do not warrant public availability (e.g., because the study was inadequately implemented), the reasons should be explained.

In addition to directing that FDA make public information about the status of study commitments, Congress should provide for the responsible reporting of study findings. As discussed in Chapter 7, the creation of an independent drug safety board and the developing of responsible procedures for making information from postmarket studies publicly available should provide some guidance on procedures for evaluating the soundness of study findings and the appropriateness of making information public. Again, an important objective is to avoid publicizing findings from studies that are badly designed, poorly executed, or inappropriately analyzed. To the extent that the agency successfully works with manufacturers on the design and execution of postmarket studies, that should also provide an important element of quality control. Criteria for public reporting should take into account manufacturer's legitimate rights involving trade secrets or certain confidential commercial information.

Recommendation 5.2: FDA's system for monitoring and reporting postmarket study commitments should include information about the disposition of study findings, for example, a change in the labeling of a device. It should also provide for the responsible and understandable reporting of the source, methods, and findings of monitored postmarket studies.

Beyond study monitoring, another step the agency should consider to increase accountability for postmarket surveillance is to provide its advisory committees with periodic follow-up information on the products they have reviewed. Such information should cover the status, methods, and findings of required postmarket studies and also include adverse event reports, safety alerts, recalls, or other actions associated with previously reviewed products. When a manufacturer is released from responsibility for information collection, the rationale should be described. This information may help advisory committees judge whether their conclusions about approval were prudent and whether their follow-up questions were reasonable.

The next chapter discusses what the committee was able to discover—given the absence of a database of study commitments—about postmarket studies relating to children's growth and development or active lifestyles. The chapter also examines some of the methodological, ethical, and practical challenges in conducting pediatric device studies.

6

Adequacy of Pediatric Postmarket Surveillance Studies

Today, Esperanza is a 30-year-old mother of two. In 1975, she was a critically ill newborn at the University of California hospital at Irvine. There, in a last-chance attempt to save her life, she became the first infant to be successfully treated with extracorporeal membrane oxygenation (ECMO), a process that allows prolonged cardiopulmonary life support. ECMO had been developed in the early 1970s to support adults with severe respiratory illness, but trial results had been disappointing. Dr. Robert Bartlett, a physician at the hospital where Esperanza was born, had been investigating ECMO with bench and animal testing for 10 years. He thought the procedure might be more successful with infants, who tend to have fewer additional medical complications than adults. By 1985, 10 years after Esperanza's treatment, death rates for infants with most of the conditions then treated by ECMO had dropped from 90 percent or more to less than 50 percent.

(Bartlett, 1985; Bartlett et al., 2000; University of Michigan, 2005)

The history of ECMO, which involves a complex system of medical devices, is interesting for a number of reasons. As suggested above, it illustrates how patient characteristics and treatment success may vary by age and how the evolution of medical innovations can have unexpected twists and turns. The technology also figured in innovative clinical trials of the device in the 1980s that are still used to illustrate ethical dilemmas in trial design (Truog, 1999). In addition, early on, medical centers using ECMO began a patient registry that has proved useful in a variety of clinical evaluations.

ECMO does not involve a fully implanted device, but patients must have vascular catheters inserted in the major blood vessels of the groin or neck. Its use typically requires days of direct contact between a child's blood and certain elements of the device system, primarily the artificial lung and the tubing that circulates the blood. As newer, less drastic treatment strategies (e.g., inhaled nitric oxide and high-frequency oscillatory ventilation) for newborn respiratory failure have shown positive short-term results

in randomized clinical trials and other studies, many centers limit ECMO to use as a rescue therapy when the center's best efforts to ventilate have failed (Truog, 1998; AAP, 2000a). ECMO also continues as a valuable last resort for infants and small children with acute heart failure who require circulatory support until heart function recovers or a heart transplant can be performed.

When successful, innovative medical devices such as those involved in the ECMO procedure can offer dramatic cures, sustain life until another therapy is available, slow the progression of disease, or ease the distress caused by an incurable condition. Long-term and even relatively short-term exposure to a device—and the surgical or other procedures associated with its use—can, however, alter a child's development in complex ways. Some of the effects may be suspected in advance, but others may be identified only through careful follow-up monitoring and evaluation. Unwanted developmental outcomes may not be evident for a number of years and thus will not be detected by short-term studies.

Chapter 2 introduced the concepts of children's growth and development and their active lifestyles and then described some of the physical, cognitive, emotional, behavioral, and social characteristics of children that may affect the design, use, and performance of medical devices. It noted that children's activities pose a risk of traumatic damage to certain implanted or attached devices. In addition, children's growth and development may affect the performance of a device. For example, growing tissues may put increased stress on some biomechanical devices. Causation may also operate in the reverse direction, that is, certain devices may interfere with children's growth.

The legislation that called for this report asked for an assessment of whether postmarket surveillance studies last long enough to evaluate the impact of growth and development for the number of years that a child has an implant. It also asked whether such studies are adequate to assess the effects of children's active lifestyles on implant longevity and failure rates. These questions reflect awareness that children's developmental characteristics may affect their experience with an implanted device. They likewise show an understanding that short-term studies of safety and effectiveness are not well suited to determine how children's growth and development may affect the performance of an implant—and vice versa. The committee interpreted its task to involve specifically an assessment of Section 522 Postmarket Surveillance studies, but it also considered other kinds of studies and sources of information.

The next section of this chapter reports the sparse results of the committee's search for postmarket studies or other information focused on the two child-centered questions identified in the legislation. The discussion then expands to consider more generally strategies for postmarket evalua-

tion of medical devices used with children. The chapter also describes some of the complexities and challenges of conducting medical device research and undertaking studies with children. It concludes with the committee's reflections and recommendations, including a recommendation that FDA be given authority to order "condition-of-clearance" studies.

FDA-REQUIRED STUDIES AND OTHER INFORMATION

As discussed in Chapter 2, problems with the potential or actual performance of devices in infants, children, and adolescents may be identified in at least three different ways (Table 2.3). They may be identified *a priori* based on a combination of expert understanding of children's developmental characteristics and detailed knowledge of the operating characteristics of a particular device as derived from theory, bench testing, simulations, and, perhaps, experience with adult use. In addition, issues or problems may be revealed as side-effects or adverse events during the clinical testing of a device with children. Subsequently, as experience with a device accumulates following its entry into the market, problems may become known through adverse event reports, through case reports or other shared clinical experience associated with normal follow-up care, or through systematic clinical or epidemiological studies, including postmarket studies ordered by the U.S. Food and Drug Administration (FDA).

Systematic studies can accelerate the identification of practices that improve outcomes for children. For example, in the 1960s, clinical observation of infants being treated for hydrocephalus led to the conclusion that cerebrospinal fluid shunt catheters placed in the atrium of the heart should be routinely revised and lengthened. The interval between placement and lengthening depended on age at implantation (e.g., a 4-month interval for shunts placed at 1 month of age and a 32-month interval for shunts placed between 8 and 12 months of age). A well-planned postmarket study that followed children for 24 months after shunt implementation could have detected this considerably earlier than the 11 years it took to accumulate and evaluate observations from clinical practice (Becker and Nulsen, 1968).

Section 522 Postmarket Surveillance Studies

Chapter 5 reported that FDA officials identified only two Section 522 Postmarket Surveillance studies that they had ordered in recent years following the approval or clearance of a medical device. Neither involved pediatric populations as such. Thus, the simple answer to the questions posed to the committee is that there are no relevant Section 522 Postmarket Surveillance studies to assess for length or adequacy. Rather than stop at

this point, the committee expanded its focus to consider condition-of-approval studies and certain other sources of information.

Condition-of-Approval Studies

The committee sought to determine whether any orders for condition-of-approval studies associated with FDA approval of premarket approval applications (PMAs) or Humanitarian Device Exemptions (HDEs) had mentioned children's lifestyle or growth and development effects. As described in Chapter 5, FDA does not now have a systematic means of identifying and monitoring condition-of-approval studies, including those studies that involve pediatric questions. During initial conversations with the committee, FDA officials reported that they did not know of condition-of-approval studies that involved pediatric questions.

Using FDA's online database of original PMA approval letters and related materials, the committee reviewed 4 years of original PMA approval letters (2001 to 2004) for a total of 168 letters. Review of these letters yielded one pediatric study associated with the approval of an injectable gel for treatment of vesicoureteral reflux (the flow of urine back from the bladder into the ureters and kidneys) (P000029, FDA, 2001). The post-approval study was to collect 5-year follow-up data on at least 180 children to assess adverse events as well as evaluate treatment outcome (reflux grade) at 3 months, 12 months, and 5 years. These outcomes were to be compared to outcomes reported in the published literature.

Nothing in the brief description of the injectable gel study indicated a specific focus on growth and development or children's activity levels, but the committee did not have access to the study protocol. The FDA panel that reviewed the PMA application raised a number of concerns about the data submitted in support of the application (e.g., those evaluating treatment outcomes in the two arms of the randomized trial knew the treatment each study subject had received) (Moodie, 2000). The panel also raised concerns about long-term migration of the gel and a slow failure rate, but it did not link these concerns explicitly to questions of growth and development or activity levels. Assuming the manufacturer completes the study, the results would not be expected until 2006.

In addition, the committee found one data collection element involving children in the 2001 letter of approval for a septal occluder device (P000039, FDA, 2001a). Post-approval reports from the manufacturer were to include data on three categories of patients, one of which was children under age 10. The letter mentioned the objective of better characterizing safety and effectiveness but nothing more specific. All other FDA information about the nature or status of the study is confidential, except that a study protocol was approved in a 2002 supplemental PMA (P000039-S001, FDA, 2002).

The committee also identified a few orders for studies that were to follow subjects who had been included in premarket studies. Some of these subjects were children, but the orders did not identify any pediatric questions.

Because supplemental approval letters are usually not accessible online, the committee was not able to systematically review them to determine whether they included provisions for further study of a device. However, while reviewing an article cited by the American Academy of Pediatrics in its statement to the IOM (AAP et al., 2004b), the committee incidentally discovered a required postmarket study associated with approval of a supplemental PMA. The article reported results from a study that FDA required when it approved a small model of a baclofen infusion pump for treatment of patients who could not be treated with a larger model (Albright et al., 2004). The one-paragraph, online summary of the approval statement does not mention this study (see P860004-S042, FDA, 1999).

According to the article reporting the baclofen study, FDA specified that data be collected for 1 year on the first 100 children implanted with the device (Albright et al., 2004). The study included 14 children who had received the implant as part of the premarket evaluation of the pump and 86 who received the implant after approval. The study found four serious system-related complications, all specific to catheters (including two catheters not made by the pump manufacturer). The authors concluded that none of the complications they observed were related to children's growth.

In addition to reviewing PMA approval letters, the committee also reviewed letters approving HDEs that mentioned use with children. It located one postmarket study involving children that was associated with an HDE for use of a left ventricular assist device with children (H030003, FDA, 2004a). The device, which had been studied with adults but not children, is intended as bridge to heart transplantation. The sponsor is to follow the first 50 children receiving the implant until transplantation, death, or other outcome. The FDA approval letter did not mention growth and development or activity considerations. For the adults implanted with the device during clinical trials, the average duration of pump support was about 3 months.

The committee also learned incidentally about one voluntary postmarket study involving children. In May 2001, when FDA cleared the first automatic external defibrillator system for use with infants and young children who experience cardiac arrest, the sponsor agreed voluntarily to conduct a follow-up study of up to 50 children worldwide to evaluate how well the device performs in actual use (FDA, 2001e). An inquiry to FDA revealed that the study was underway, but FDA would not provide other information on grounds that such details are statutorily protected confidential information (personal communication, Thomas P. Gross, M.D., Director, Division of Postmarket Surveillance, CDRH, October 21, 2004).

Premarket Clinical Studies

The focus of this report is on postmarket surveillance, but for the certain devices and conditions, the possible value of postmarket studies of growth and development questions may be related to the length and other features of premarket studies. Premarket studies usually focus on short-term outcomes. The summaries of safety and effectiveness published with PMA approval statements may, however, include contraindications or cautions related to growth or development or activity level concerns that are evident even without clinical study. Examples involve implants that are clearly too large for small children or orthopedic devices that will obviously interfere with bone growth.

Conversations with FDA staff and committee review of individual device approvals indicate that clinical studies to support approval or clearance of medical devices generally last 1 to 2 years. Individual research participants may be followed for shorter periods if, for example, patients are entered into the study at different times following diagnosis.

Occasionally, FDA specifically asks sponsors of a PMA to accumulate study data for considerably longer periods than usual. A case in point involves the Vertical Expandable Titanium Rib (VEPTR) implant that recently received a Humanitarian Device Exemption from FDA for use with children suffering from thoracic insufficiency (defined as severe deformities of the chest, spine, and ribs that prevent normal lung development and respiratory function). The implant must be surgically adjusted to accommodate children's growth approximately every 6 months, which means that a child implanted at age 3 could expect to undergo at least 28 surgeries by age 17. When the sponsor approached FDA about approval for the device, FDA requested long-term safety and effectiveness data on children who received the implant. The sponsor eventually submitted data for a prospective case series of 247 children, some of whom had been followed for 14 years (H030009, FDA, 2004b). The FDA summary of safety and probable benefit did not report the average follow-up period, but an article describing results for 27 of 41 children implanted since 1990 reported an average follow-up period of 5.7 years (range, 2 to 12 years) (Campbell et al., 2004). No condition-of-approval studies were specified by FDA in the HDE approval letter. The sponsor is, however, planning to create a registry and organize a study group (involving the eight hospitals that participated in the multi-center study of the device) to monitor treatment and adverse events and plan prospective studies using the registry (personal communication, Robert Campbell, M.D., Professor of Orthopedics, University of Texas Health Science Center at San Antonio, November 8, 2004).

As described by the primary investigator, the premarket clinical studies

of VEPTR showed expected problems (based on experience with other treatments) related to the need for multiple surgeries (personal communication, Robert Campbell, M.D., Professor of Orthopedics, University of Texas Health Science Center at San Antonio, November 8, 2004). The studies also found migration of the device over longer time periods as a function both of the pressure exerted by the device and the child's growth. In response to experience during premarket investigation of the device, several changes were made in the design of the device as shown in Figure 6.1. In addition, the study identified the surgical challenges in safely using the device. The first line in the draft professional labeling approved by FDA states "IMPORTANT: Prior to use, the physician should be trained in the surgical procedure recommended for the use of this device" (H030009, FDA, 2004c, p. 1).

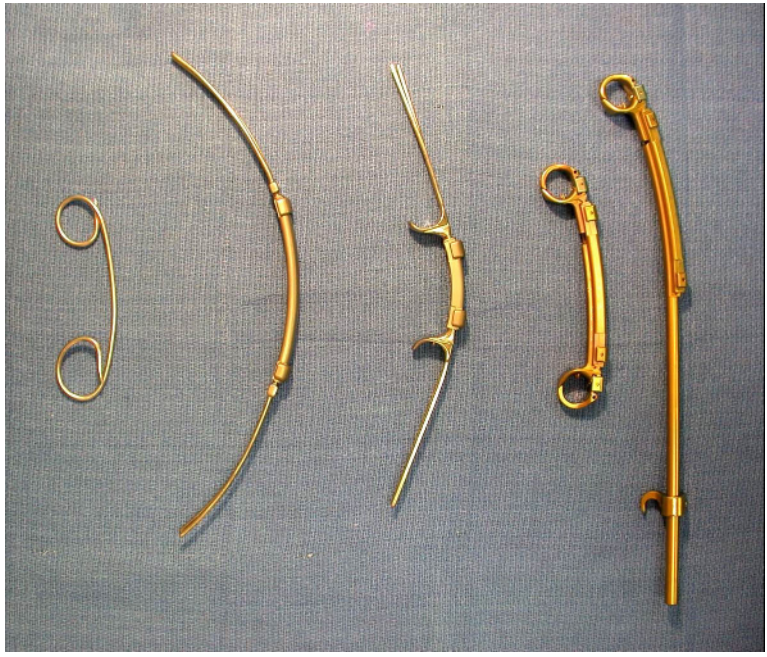


FIGURE 6.1 Evolution of the Vertical Expandable Prosthetic Titanium Rib (VEPTR) showing versions from 1987, 1989, 1991, and 1996. (The rightmost item shows the device in its expanded mode, to its left is the unexpanded device.) (Courtesy of Robert M. Campbell, M.D.)

Safety Advisories and Adverse Event Reports

As an additional step, the committee investigated FDA safety advisories and similar information to determine whether any appeared to have been prompted by adverse event reports associated with children's activity levels or growth and development on device longevity or performance. The committee found some advisories based at least in part on adverse event reports involving children, but none of the reports obviously involved problems arising from children's activity levels or growth and development. For example, a public health notification on the risk of bacterial meningitis in children with cochlear implants did not cite developmental considerations explicitly. It stated, however, that it focused on young children "because they account for the majority of known meningitis cases and represent the population that will receive most cochlear implants in the future" (Pressly, 2003, p. 2). The study that investigated the meningitis risk and led to the notification is discussed further below.

Searches of the FDA's Manufacturer and User Facility Device Experience (MAUDE) database yielded some examples of adverse event reports that might be attributed to children's activities. For example, use of "basketball" as a search term produced a few potentially relevant reports of incidents involving people playing basketball, although the public database available to the committee did not allow determination of whether these incidents involved children.

The committee concluded that a more systematic search of the MAUDE database was not feasible because the array of possible "active-lifestyle-related" events and possible narrative descriptions of such events is very large, and no recognized nomenclature exists to characterize them. In any case, although FDA has evaluation codes for manufacturers to characterize their evaluation of an adverse event, the agency offers only four very general codes related to use or behavioral factors, for example, "user error caused event" (FDA, 2001j, p. 4). Other patient and device codes are also not specific for lifestyle-related events. In sum, if the narrative for an adverse event report said something like "problems with implant functioning arose after the child jumped off the sofa and bumped her head," no existing code or feasible search strategy would identify this incident as related to children's active lifestyle.

Similar difficulties limit the feasibility and value of searching the database for reports that might identify adverse events related to growth and development. For example, reports of a device migration (for which several codes exists) may be related to many factors not related to growth and development. (One device code, 1272, indicates that a device will not support growth [FDA, 2001b].) The committee concluded that further examination of adverse event reports would not be useful in assessing whether

pre- or postmarket studies "last long enough" to identify problems related to active lifestyles or growth and development.

Voluntary Postmarket Studies

In addition to identifying studies required by FDA, the committee made some effort to locate other medical device studies that considered children's active lifestyles or their growth and development. Unfortunately, the committee found it difficult to identify such investigations. With respect to lifestyles in particular, literature searches and inquiries to clinicians and researchers yielded little—although undiscovered studies of the impact of children's activities on devices certainly may exist. For example, clinical studies have the potential to identify "active-lifestyle" issues incidentally in the course of investigations that track health and functional outcomes. Unless quite striking, however, the committee concluded that such incidental findings are unlikely to be identified in publication abstracts, key words, or other search aids.

With respect to growth and development, the committee determined that locating relevant clinical studies would, by and large, require device-by-device or condition-by-condition literature searches and device-by-device and condition-by-condition considerations of whether possibly relevant studies are "of long enough duration" to evaluate the impact of child's growth and development on the performance of an implant *or* to assess the effects of an implant or other medical device on the way a child grows and develops. Such a search strategy was beyond the committee's resources. Based on member knowledge, inquiries to pediatric specialists, and literature searches, the committee did identify several relevant studies. Some of these studies are cited in this and other chapters.

DIMENSIONS AND COMPLEXITIES OF MEDICAL DEVICE RESEARCH

Studies of medical devices—especially clinical studies—present challenges both before and after market approval or clearance. In contrast to drugs reviewed by FDA, devices are more often works in progress—subject to minor, modest, or major modifications during both premarket and postmarket clinical studies. Congress has recognized this aspect of device innovation with special provisions to reduce certain regulatory burdens on sponsors (21 USC 360j(g)(6)).[1] Depending on the nature of a change during the

[1]21 USC 360j(g)(6) (see also 21 CFR 812.35) provides

(A) Not later than 1 year after November 21, 1997, the Secretary shall by regulation establish, with respect to a device for which an exemption under this subsection is in effect,

course of a study, data may need to be reported and analyzed separately as well as together. Such challenges may be particularly daunting for the small companies that are a more prominent feature of the device industry than the drug industry.

Although specifics will vary depending on the device, premarket testing of medical devices that require clearance or approval may entail a series of evaluations that usually involve nonclinical *in vitro* testing (also called laboratory or bench testing) and that may extend through tests with animals, possibly cadavers, and then humans. Postmarket studies may also use one or more of these evaluative strategies.

To illustrate the kinds of pre- and postmarket testing that a complex implanted device may undergo, Box 6.1 summarizes the testing of the Amplatzer atrial septal occluder, which, as described earlier, was granted approval for marketing in 2001 (P000039, FDA, 2001a). The device was tested in both children and adults (overall mean age of 18), and results were compared to a nonrandomized, mostly prospectively identified group of individuals (mean age of 6) who were treated surgically. A second small comparison group included patients who were followed through a registry. The FDA summary of safety and effectiveness did not break out study results by age. As described earlier, the approval order for the device included provisions for further postmarket study.

Many devices are proposed for FDA approval as effective for a specific task (e.g., to remove clot from an artery) rather than for a specific therapeutic intervention (e.g., preventing damage to the tissue supplied by the artery). This approach allows a device to become available as a tool with many potential clinical applications and also tends to simplify the premarket evaluation process.

---

procedures and conditions that, without requiring an additional approval of an application for an exemption or the approval of a supplement to such an application, permit—

(i) developmental changes in the device (including manufacturing changes) that do not constitute a significant change in design or in basic principles of operation and that are made in response to information gathered during the course of an investigation; and

(ii) changes or modifications to clinical protocols that do not affect—

(I) the validity of data or information resulting from the completion of an approved protocol, or the relationship of likely patient risk to benefit relied upon to approve a protocol;

(II) the scientific soundness of an investigational plan submitted under paragraph (3)(A); or

(III) the rights, safety, or welfare of the human subjects involved in the investigation.

(B) Regulations under subparagraph (A) shall provide that a change or modification described in such subparagraph may be made if—

(i) the sponsor of the investigation determines, on the basis of credible information (as defined by the Secretary) that the applicable conditions under subparagraph (A) are met; and

(ii) the sponsor submits to the Secretary, not later than 5 days after making the change or modification, a notice of the change or modification.

BOX 6.1
Example of Medical Device Testing: Atrial Septal Occluder

Preclinical study
- Bench testing for strength and reliability
- MRI compatibility
- Corrosion (bench and animal testing)
- Biocompatibility
- Sterilization/shelf life
- Live animal testing in minipigs

Premarket clinical study
- Multi-center, nonrandomized, controlled study to evaluate safety and effectiveness compared to surgical intervention
- Noncomparative registry study

Postmarket condition-of-approval study provisions
- Five-year follow up of subjects enrolled in phase IIB of the trial
- Data to be obtained from trial or additional individuals who (1) have device sizes greater than 28 mm or less than 10 mm, (2) residual shunts >2 mm, or (3) were under 10 years of age when the device was implanted.

SOURCE: P000039, FDA, 2001b; P000039-S001, FDA, 2002.

Most of the remainder of this section will consider device research strategies and challenges. Some constraints on research, however, relate less to methodological or technical challenges than to marketing or financial concerns. For example, as is true for other medical products, once a device is approved or cleared, a manufacturer may not be enthusiastic about studying additional uses or populations because such studies could provide negative information that could, in turn, lead to labeling restrictions or even market withdrawal.

If the use of a device is not restricted, medical practitioners can adopt new "unlabeled" uses without oversight by FDA (as described in Chapter 3). Such use is sometimes based on small case series of individual or medical center experiences that are reported at national or international meetings and then followed by diffusion to other centers. For a device with an approval that is not restricted to an adult population, a study with children could generate negative information that might prompt such a restriction. Particularly if the pediatric market is small, a manufacturer might prefer simply to label the device as not indicated for use with children rather than offer or agree to conduct a pediatric study. Given that manufacturers may be reluctant for various reasons to support such studies, other sponsorship and funding for such studies is important (as is the availability of clinicians and other

personnel with sufficient expertise in device studies). The evidence base for practice could benefit from increased clinician involvement in more systematic clinical studies of devices (Moss et al., 2001; Curry et al., 2003).

Even with interest and resources, others barriers to postmarket study may arise. Investigators may find it difficult to recruit participants for clinical trials of devices that are approved (or cleared) and available for use without restrictions. Such trials often make demands on participants (e.g., for extra testing and visits) that go beyond those associated with standard clinical use of the device. In addition, postmarket follow-up studies may be less attractive to research funders and medical journals than studies undertaken for original market approval of innovative device. For these and other reasons, academic investigators may not find involvement in postmarket studies to be professionally appealing.

To cite a practical complication that is not restricted to device studies, the committee understands that manufacturers sometimes have difficulty collecting data for postmarket studies based on professional or institutional concerns about the privacy provisions of the Health Insurance Portability and Accountability Act (HIPAA). For example, some providers may strip patient-identifiers from the information they provide, which makes it difficult or impossible to aggregate information about the same patient from multiple providers. Chapter 4 encouraged FDA to continue its efforts to educate providers about HIPAA and the legality and value of providing information to support postmarket device surveillance, including postmarket studies.

Study Designs and Information Resources for and from Postmarket Devices Studies

A substantial literature exists on the characteristics and merits of various designs for clinical research. These discussions often focus on or assume drugs as the intervention being investigated. Possible constraints on the use of study designs to investigate the safety or effectiveness of medical devices may not be considered. This brief review of study designs is intended to further illustrate the options and challenges of medical device studies. Appendix D discusses in more depth the objectives, characteristics, and limitations of major study designs and data analysis techniques (e.g., data mining).

Some study designs are *experimental*, which, as used here, means that an investigator controls the use of the intervention(s) being studied.[2] Ex-

[2]For reimbursement purposes, the Centers for Medicare and Medicaid Services makes a distinction between "experimental" device types and "nonexperimental/investigation" device types. The former, which are not reimbursable, are basically devices for which initial questions of safety and effectiveness have not yet been answered (DHHS, 1995). This is a much more restrictive use of the term than that employed here.

perimental designs are necessarily prospective, that is, individuals are followed forward in time to assess outcomes. When the investigator does not control the use of the intervention being studied, designs are termed *observational*. Such studies are sometimes prospective but more often retrospective, that is, based on information already existing in medical records, billing databases, or other sources. The brief overview below starts with experimental studies, not because they are commonly used for postmarket studies of medical devices but because they are considered the benchmark for valid evaluations of clinical care.

Experimental Studies

When designed and implemented properly, the randomized trial is generally held to provide the strongest evidence about the safety and efficacy of a medical intervention.[3] In such a trial, investigators use explicit randomization procedures to assign individuals to study groups, for example, an intervention group that will be compared to a group receiving "usual" care or, less often, a group receiving another specific intervention (e.g., an alternative medical device). Randomized trials have occasionally been used to compare medical devices used with children, for example, programmable versus conventional shunts for individuals with hydrocephalus (Pollack et al., 1999).

When entry into study groups is not random, opportunities arise for biases or baseline differences in groups to compromise the validity of study comparisons. Various statistical techniques may help in assessing or controlling for biases, but these are weaker tools than random assignment.

Ideally, to limit bias in the reporting and assessment of outcomes, the assignment of study participants to different groups will be *blinded,* that is, it will not be known either to the investigators or to individuals being studied. (Unlike such "double-blinded studies, a study is termed "single blinded" if only the evaluator or only the study subject is unaware of the intervention.) The strategy of blinding is difficult if not impossible for many device studies. For example, if use of an implanted device is compared to an accepted medical therapy, individual assignments will usually be obvious to both investigators and study participants. On occasion, investigators have devised "sham" or placebo procedures (e.g., making a shallow surgical incision or arranging exposure to a nonfunctioning device) to limit this source of bias, but such options typically face more ethical and practical barriers than is the case with placebo use in drug studies (Clark and

[3]As described in Chapter 1, the term *effectiveness* may be used to describe the achievement of desired results in actual practice with the term *efficacy* reserved for the achievement of such results in controlled studies.

Leaverton, 1994; Freeman et al., 1999; Albin, 2002). For certain devices, it may be possible to randomize patients to be assessed with the device operating (turned on) or not operating. In general, however, it is necessary to recognize that strategies that may be appropriate and feasible for drug studies may not be appropriate or feasible for device studies.

An example of a randomized, single-blind, long-term postmarket study of device safety is the Children's Amalgam Trial, a randomized trial of safety that compares silver amalgam dental restorations with a mercury-free restorative material for children aged 6 to 10 (Children's Amalgam Trial Study Group, 2003). This study, which was not required by FDA, is funded by the National Institute of Dental and Craniofacial Research at the National Institutes of Health (NIH). Originally, intended to last 5 years, the study has been extended to 10 years. The outcomes of interest include neuropsychological development and renal functioning. Those involved in measuring the outcomes do not know the assignment of study participants.

Some studies are prospective and comparative but not randomized. For example, a study might be designed to recruit children for research on an innovative device at one medical center while one or more other institutions might prospectively follow children receiving a common alternative form of care. (Parental permission would be necessary for both groups, and recruitment and other aspects of study design should be as comparable as possible.) This approach, while increasing the opportunity for important nonrandom differences in study groups and their evaluation, may make sense in certain situations, for example, when the use of a new device involves a significant "learning curve" for clinicians who must master a new surgical technique.

The phenomenon of the learning curve points to another complexity of device trials. Unlike the administration of many drugs in clinical trials, the use of an implant or other device in a trial may depend on a surgical or other procedure that requires new skills or involves unusual elements that must be learned. Differences in skill levels among those "administering" a device intervention can compromise study findings. Thus, some surgical trials have set technical performance standards for participating surgeons (Ferguson et al., 1999). In addition to compromising the validity of study comparisons, differences between clinicians in a trial and clinicians in practice may also limit the generalizability of study findings beyond the research setting.

Often, clinical studies of devices involve neither randomization nor a prospectively followed control group, and such studies can be considered experimental only by the narrow criterion that access is controlled by the investigator. "Single-arm" trials may employ a prospective assessment of a single intervention, access to which is determined by the investigator. Retrospective comparisons are made either to the subject's status prior to the

intervention or to other individuals (historical controls) for whom information is available in medical records, published materials, or other sources. The former strategy works best when the before-and-after measures for study subjects are standardized and complete, when the natural history of the condition is well-described, and when a "placebo effect" is considered unlikely. The use of historical controls presents many opportunities for bias. For example, depending on the data source for the historical controls, the methods used to collect and record data on key variables may be unstandardized, poorly documented, or unknown. Information that would normally to be used to compare baseline or other differences between groups may simply be missing. Literature reviews suggest that single-arm trials are more likely than comparative controlled trials to conclude that an intervention effect exists (Pocock, 1993).

When FDA approves a device, it may direct a device manufacturer to continue to follow prospectively the individuals who participated in the study that was used to secure FDA approval of the device. If the study originally involved both intervention and control groups, both cohorts would, ideally, be followed.

Some have argued for increased support for pragmatic or practical clinical trials that are designed specifically to answer questions faced by decision makers (see, e.g., Tunis et al., 2003). Such trials would include diverse populations and practice settings and evaluate a range of clinical and functional outcomes. If such practical clinical trials included medical devices used with children, they could help narrow the knowledge gaps that especially characterize pediatric use of many medical devices.

Observational and Other Study Designs

Many device studies involve observational designs, in which access to an intervention or comparison group is not under an investigator's control. The most ambitious (and, usually, expensive) such studies are prospective and comparative. For example, a study may follow groups (cohorts) of children who—by family choice or other determinant not under the investigator's control—are treated or are not treated with a device. Long-term, diagnosis-based registries can help investigators identify and monitor children for prospective, comparative observational studies. (Registries are discussed further below.)

When FDA directs a manufacturer to follow the first 50 (or some other number) individuals treated with the device after marketing approval, it is ordering a noncomparative, observational study. The left ventricular assist device study cited above is an example of such a study; it involved a previously unstudied group (children). Although weaker than a controlled experimental study, this kind of planned, prospective observation has the

potential to identify unanticipated safety problems earlier than they would emerge from usual clinical practice.

Most observational studies are retrospective. They depend on existing information (secondary data) to identify study subjects and provide relevant data about their past use of a device and other variables. Again, long-term, diagnosis-based registries may be helpful in identifying individuals for study.

One type of retrospective study design, the case-control study, is particularly useful for investigating rare outcomes. This type of study matches cases (e.g., children with a device who have experienced an adverse event) with controls (e.g., children with a device who have not experienced the event). One component of the postmarket investigation of cochlear implants and meningitis cited above was this kind of case-control study (Reefhuis et al., 2003). Initial sources of information for the study were warranty lists (a limited kind of registry) from implant manufacturers and adverse event reports or other data that identified cases of meningitis in children with cochlear implants. Not all the information was historical. Parents of the children who were identified from warranty lists (which were said to be 95 percent complete) and other sources were contacted for additional information about factors that might have put their child at risk for meningitis (e.g., type of implant, previous diagnosis of meningitis, placement of a ventriculoperitoneal shunt).

Another example of an observational study involving cochlear implants is a study conducted by Waltzman and colleagues that assessed the long-term effects of electrical stimulation (Waltzman et al., 2002). They reviewed the experience of 81 children who had received cochlear implants and had been followed for 5 to 13 years.

Less common and quite different from the prospective and retrospective studies described above are autopsy studies. Such studies can identify physiologic changes not otherwise detectable. Such findings may suggest the need for closer monitoring of certain patient characteristics or adaptations in a device or aspects of its use. Fortunately, child deaths are relatively uncommon, and many critically ill children treated with innovative medical devices survive into adulthood. Nonetheless, despite the stress on families of children who die, future children and families can benefit from sensitive efforts to encourage autopsies.

Parenthetically, although studies of retrieved devices are not clinical studies and although the opportunity for the retrieval of implanted devices is usually not related to a child's death, it is worth reiterating the argument made in Chapter 4 for systematic study of retrieved devices. Manufacturers and others can accumulate important information from retrieved implants and other devices as part of a comprehensive process of observation, testing, and evaluation once a device has been marketed. This information can

be put to use to improve product reliability or durability and also advise clinicians and patients about the potential for problems that might otherwise not be anticipated.

Registries as Resources for Postmarket Device Studies

As defined in Chapter 1, a registry is a system for collecting information about a class of individuals or patients who have in common a disease, injury, condition, medical procedure or product, or similar characteristic. Registries vary considerably in the amount of information they contain about patients and their care. Manufacturer registries may include only information needed to locate patients in case of a recall, or they may—when designed to support a postmarket study—include considerable clinical information. Although FDA is supportive of other registry studies such as those organized by professional societies, the agency's primary focus is on registries associated with postmarket studies that they have required or voluntarily negotiated with manufacturers.

Some registries are diagnosis-based and include information about people with a diagnosis who receive certain interventions and people with the diagnosis who do not. Other registries include only individuals who have received a device or intervention. Although a registry managed by a single manufacturer normally would track a single device, an intervention-based registry developed by a professional society or other cooperative group might offer the opportunity to compare different devices or different procedures for using a device. To the extent that centers participating in cooperative intervention-based registries have the most successful programs and the most experienced clinical teams, their results may not be representative of average experience and average complication rates.

An example of a diagnosis-based registry is the pediatric cardiomyopathy registry that is funded by the National Heart Lung and Blood Institute and managed by the New England Research Institute. The registry covers children in the United States and Canada who have been diagnosed with cardiomyopathy since 1990 (NERI, 2004; see also Felker et al., 2000; Harmon et al., 2004). Its aims include estimation of the incidence of the condition (in two geographic regions), better understanding of cardiomyopathies, describing their course and treatment, and identifying correlates of successful patient management. The registry includes 100 clinical sites and records for about 2,500 patients.

An example of an intervention-based registry is the Extracorporeal Life Support Organization (ELSO) registry, which is managed by the University of Michigan. (Extracorporeal Life Support or ECLS is the term that the organization uses for the procedure that historically and earlier this chapter has been referred to as ECMO.) About 110 participating centers in 14

countries submit information to the registry, which includes data on patients until death in hospital or hospital discharge (University of Michigan, 2005). The purpose of the registry is to help define the patient populations treated with the procedure (including specific medical problem), and describe the treatment they received.

The ELSO registry supports retrospective assessments of short-term outcomes and complications as they relate to patient and treatment characteristics. When participating institutions follow or maintain postdischarge contact with a high percentage of their ECMO patients, they can combine the registry data with additional medical record data and new assessments of patients to assess longer term outcomes.

Given the cost and complexity of long-term, multisite studies, it is not surprising that most examinations of longer term ECMO outcomes appear to have involved single centers (see, e.g., Glass et al., 1997; Graziani et al., 1997; Ahmad et al., 1999). In the United Kingdom, however, a multicenter collaborative group is conducting follow-up evaluations of ECMO-treated children at ages 1, 4, and 7 (UK Collaborative ECMO Group, 1998).[4]

Another intervention-based registry is the Pediatric Heart Transplant Study (PHTS). Until recently, this group was a self-funded collaboration between approximately 20 pediatric heart transplant centers in North America (personal communication, Richard E. Chinnock, M.D., Professor of Pediatrics, Loma Linda University School of Medicine, February 1, 2005; personal communication, Steven A. Webber, M.B.Ch.B., Associate Professor of Pediatrics, University of Pittsburgh School of Medicine, February 1, 2005). The registry began in 2003 but has data extending several years before that. Each center contributed $2,000 to the project and donated the time of personnel to fill out the forms, and the University of Alabama at Birmingham hosted the database. The group has been able to obtain outside funding for some studies, including a study of ventricular assist devices as a bridge to transplantation, but funding for major studies is an ongoing concern.

The experience of the PHTS suggests that the creation of registries, at least for uncommon events, can be initiated without large, direct financial commitments as long as sufficient volunteered expertise is available to

[4]In the United States, researchers at an ELSO-participating institution recently proposed an assessment of the long-term effects of children's exposure to di(2-ethylhexyl) phthalate (DEHP, a substance that makes plastic tubing more flexible) during ECMO (personal communication, Billie L. Short, M.D., Director of Neonatology, Children's National Medical Center, Washington, DC, January 12, 2004; see also AAP, 2003, Shea et al, 2003). The assessment would include registry data for 12 early ECMO centers and build on an initial single-center study that included physical examinations of 19 adolescents who had undergone ECMO as neonates (Rais-Bahrami et al., 2004).

construct and maintain the registry until it can establish itself. The committee encourages greater involvement by professional societies in stimulating and supporting the design and establishment of device-relevant registries, but it also recognizes that the growth of well-designed registry-based studies requires support and encouragement from research funding agencies such as NIH. NIH has, in the committee's experience, only reluctantly supported registries and then primarily to encourage the orderly transition of a new technology into clinical practice. Ideally, a registry to support clinical studies would be managed by an independent third-party, but the funding for such outside management may only be forthcoming after a registry has been created and shown promise.

Large Automated Patient Databases as Resources for Postmarket Device Studies

Developments in medical informatics have created important, new sources of long-term medical information that make it feasible to monitor device safety—and population health more generally—in ways that were previously not feasible or affordable. These sources include both inpatient databases and databases with inpatient and outpatient information for large populations, for example, health maintenance organizations (HMO) members or Medicare or Medicaid enrollees.

In addition to potential uses in the surveillance of adverse device events and device hazards, electronic inpatient databases may be fruitful for certain postmarket device studies. For example, observational studies based on such databases have investigated common problems with devices to treat hydrocephalus, although the databases have not allowed researchers to distinguish different types of shunts or different manufacturers (see, e.g., Cochrane and Kestle, 2003; Smith et al., 2004).

Some hospitals have cooperated to create multi-institutional automated databases. For example, the Child Health Corporation of America (CHCA, a business alliance of 42 children's hospitals) has created, among other activities, a Pediatric Health Information System that includes certain clinical and financial information and an extensive data checking process to assure data quality (Fletcher, 2004). The database can support some device safety studies, but the system currently captures only limited information about types of devices (e.g., from itemized bills) and device-related events (e.g., based on ICD-9 codes for certain device-related complications and malfunctions).

Individual hospital databases may include more complete device information, for example, when electronic medical records include data scanned from device and patient armband barcodes in addition to detailed clinical

information. Such databases, especially if expanded to hospital networks with large numbers of children, could provide a useful resource for certain pediatric device safety studies because they would provide greater specificity about device type, more relevant clinical details, larger numbers of children with characteristics of interest, and a denominator for safety and adverse event analyses.

Compared to hospital-only sources, large automated billing and medical record systems maintained by some HMOs and other entities offer the advantage of including data on both inpatient and outpatient care. Unfortunately, as is often the case for inpatient-only databases, detailed information about devices is frequently not available because use of a device is subsumed in another, broader event or transaction such as billing for a medical or surgical procedure. Moreover, as discussed earlier, current device coding options are often insufficient to identify the brand or model of a device implicated in an event. Without such codes, a strategy based on review of computer-based medical records cannot automatically link event reports to specific devices, although the significance of coding limitations varies among devices.

The difficulties for device surveillance and epidemiology created by coding limitations is captured by the following comment by a researcher on problems encountered in determining the specific model of an ultrasound device used for many obstetrical patients, even though investigators knew when and where the procedure occurred. "We needed to contact each obstetrics office and ask a busy person to find and read to us the make and model information, [and] since some offices had more than one model, we couldn't assign their patients to specific devices" (personal communication, Richard Platt, M.D., Harvard Medical School and Principal Investigator, HMO Research Network CERT, April 8, 2005). This comment reflects experience in the HMO Research Network, which is one of the Centers for Education and Research in Therapeutics (CERTs), a program created by the FDA Modernization Act of 1997 and overseen by the Agency for Healthcare Research and Quality (AHRQ). The network, which includes 14 large HMOs, is conducting several retrospective cohort studies of drug safety and medication errors. Past studies have investigated the association between certain nonsteroidal anti-inflammatory drugs and serious coronary problems (Ray et al., 2002). Device studies have proved substantially more difficult for the Network (personal communication, Richard Platt, M.D., Harvard Medical School and Principal Investigator, HMO Research Network CERT, December 9, 2004; personal communication, James Donahue, Ph.D., Project Scientist, Epidemiology Research Center, Marshfield Clinic Research Foundation, December 9, 2004). In conversations with experts from the Network and other investigators working with large database systems in the CERTs program and elsewhere, the committee found

that none had undertaken a record linkage study involving devices, and all of them reported limitations with existing databases.

In some circumstances, studies involving a medical device used with children could take advantage of ad hoc "hands-on" or manual processes to record device exposures or unusual situations for which the normal data collection process does not suffice (personal communication, Alexander Walker M.D., Dr.P.H., Chief Scientific Officer, Ingenix, March 9, 2005). Thus, children could, in principle, be manually "flagged" as having undergone a procedure or received a device of public policy interest or concern, and then the flagged cohort could be linked to information in automated practice databases. Thereafter, follow-up information would be collected by normal procedures.

AHRQ recently announced that it planned to fund a new CERT that would focus on medical devices (Rundles, 2004). This is a positive step and may focus more attention to the problems identified in this report.

Adequacy of Reporting of Information from Device Studies

Even when clinical studies of medical devices are undertaken, the reporting of key information about the study procedures and outcomes is often too limited to assess the results or the quality of the research procedures that produced them. For example, the summary information of safety and effectiveness published with approvals of PMAs is helpful, but the summaries are not easy to review and they vary in how fully and clearly they describe key aspects of the studies. Some studies may generate more complete descriptions in the peer-reviewed literature, but these must be found through an independent search.

In contrast to the PMA summaries, many peer-reviewed published studies follow a standard reporting format intended to improve the reporting of data and statistical methods for clinical trials. The standard, known as CONSORT (Consolidated Standard of Reporting Trials), has been accepted by many leading medical journals (see, e.g., Begg et al., 1996; Liem et al., 1997; Meinert, 1998; Moher, 1998; Moher et al., 2001). The epidemiology community has been developing a similar set of guidelines, STROBE, which stands for Strengthening the Reporting of Observational Studies in Epidemiology (see, STROBE, 2005).

FDA should consider revisions in the format of PMA summaries to make them more consistent with the CONSORT reporting format. Such a shift would make it much easier for readers to understand the methods used to generate the data submitted to FDA and to evaluate the limitations of these methods and, thus, the limitations of the evidence on which FDA is basing its decisions. A revised format might also direct attention to aspects of device studies that could be improved.

Device Epidemiology as an Underdeveloped Field

Both better data resources and improvements in observational research methods are needed to support epidemiologic studies tailored to the special challenges posed by medical devices. (see, e.g., Shatin et al., forthcoming). The field of device epidemiology can build upon the lessons learned in the related field of pharmacoepidemiology. Over the past 20 years, universities have developed pharmacoepidemology research centers and other programs to offer training and grant degrees. These programs have helped to produce a substantial cadre of research scholars to conduct drug epidemiology studies. As the value of such studies has been recognized, manufacturers and contract research organizations have built their own pharmacoepidemiology units. With this growth, a distinct profession has emerged with its own international professional organization, the International Society for Pharmacoepidemiology (ISPE).

Currently, the committee does not see the same momentum to advance device safety epidemiology. This perpetuates an unfortunate cycle involving an insufficient knowledge base, a shortage of solid research proposals, limited funding for research, and thus, little new knowledge on which to build further research or support for major programs of structured epidemiologic monitoring of device safety.

FDA staff have recognized the importance of device epidemiology and methods development and have contributed in this area. Contributions from other agencies and from university- and industry-based methodologists are important to supplement FDA's limited resources. One encouraging step is the creation within ISPE of a special interest group for device epidemiology, which may provide a forum to promote the advancement of the field. Another useful step would be for centers with expertise in epidemiology and therapeutics need to offer education in medical device safety studies. In addition, agencies that fund the therapeutics research and education infrastructure (AHRQ, NIH, and the Centers for Medicare and Medicaid Services, in particular) should likewise support the development work necessary to expand the core capacity for epidemiologic research on device safety. Combined with more precise recording of device information in the patient record, these steps should reduce the barriers to needed long-term postmarket studies of medical device safety and effectiveness.

SPECIAL CHALLENGES OF RESEARCH INVOLVING CHILDREN

Beyond the general challenges of conducting ethical, scientifically valid human research and the particular challenges of evaluating medical devices, those interested in developing and testing medical devices to fit children's

developmental needs and characteristics face some additional constraints (see, e.g., IOM, 2004a; FDA, 2004p). In brief, they include the following.

- *Small populations.* Because children are much less likely to suffer ill health than adults, the population of children with a particular health problem may be quite small. As a result, investigators may find it difficult to enroll enough children to make some postmarket research feasible, even more so if one objective is to make statistically valid comparisons of safety or effectiveness in relevant subgroups (e.g., infants and young children or boys and girls). Because enrolling sufficient numbers of children tends to be more difficult than enrolling adequate numbers of adults, pediatric studies are likely to require more study sites and more time. This increases the complexity of planning, funding, and implementing such studies, which may be a particular deterrent to commercial sponsors of research.
- *Special regulatory and ethical protections for child research participants.* Certain research that is ethically acceptable and permitted with adults may not be acceptable with children (see, e.g., NHRPAC, 2001; IOM, 2004a). FDA and other regulations of the Department of Health and Human Services (DHHS) limit the level of risk to which children can be exposed in research supported, conducted, or regulated by DHHS (21 CFR 50 and 56; 45 CFR 46). For healthy children, who researchers may want to use as a control group in a study, the level of risk may be no more than minimal. For children who have a medical condition or problem, the level of risk can be only slightly above minimal unless the research has the prospect of benefiting them. These rules limit, for example, the use of certain kinds of invasive studies that are done solely to collect physiologic information.

Under special regulatory provisions, the Commissioner of FDA can approve pediatric studies of special importance that could not otherwise be approved under research protection regulations (21 CFR 50.54). As noted in Chapter 2, the American Thoracic Society provided an example of study that might be appropriate for such consideration. It noted that "[s]tudies of [nebulized] drug deposition to the infant, toddler, or children with tracheostomies are rarely performed in the United States due to the requirement for radiolabeled drug markers" (ATS, 2004b, p. 3). Such investigations are considered to involve more than minimal risk without prospect of benefit to the children being studied. The ATS, however, questioned whether it was ethical to use the devices without allowing testing in infants and children to determine whether the devices were actually delivering therapeutic levels of drugs to these populations. Thus, such studies are candidates for review by the Commissioner.

- *Lack of child-relevant outcome measures and norms.* Because mortality rates for children are generally low, other outcomes measures become more important for assessing the quality of pediatric care and the safety and

effectiveness of interventions. Sometimes effectiveness requires comparison to normal values of a variable (or usual values for a patient with a particular condition), but these values may not be available for children. An example involves the use of ventilator utilization rates to assess the effectiveness of neonatal intensive care interventions and units. Until recently, reference data were not available to allow risk-adjusted comparisons that take into account differences in the severity of patient condition and baseline risk of needing assisted ventilation and lengthy ventilation (Wilson et al., 2000; see also AAP et al., 2004b).

- *Parent factors*. Parents of desperately ill children may see a clinical trial as the last chance for their child. If opportunities exist to obtain an experimental intervention outside a trial—and particularly if the trial has a control arm that involves assignment to a placebo or usual care—then parents may seek out those nonresearch opportunities, perhaps more vigorously than they would for themselves. In addition, with older children in particular, parents and children may be in conflict about enrollment in a study. In most situations, the parent must give permission for child's inclusion in research, but a child's assent is not necessary when research presents a prospect of directly benefiting the child. Depending on the circumstances, however, researchers may be reluctant to override a child who does not want to participate, even when a child's assent is not required.
- *Institutional and professional factors*. Many pediatric studies will require multiple centers with a sufficient patient base and a research infrastructure that can support such studies. A model for such multi-institutional studies is the Children's Oncology Group, which includes over 240 institutions in the United States and other countries and receives support from the National Cancer Institute. Estimates vary but a majority of children with cancer are thought to be enrolled in clinical studies (IOM, 2004a). The model for pediatric cancer studies cannot be moved wholesale to medical devices, which involve a very broad range and diversity of pediatric health problems, devices and associated procedures, and professionals. Nonetheless, the clinical research networks funded by the National Institute for Child Health and Human Development and other NIH units might be better utilized to support the systematic assessment of medical devices used with children. In addition, surgical and device-oriented specialties should be encouraged to place greater value on the systematic evaluation of medical devices and associated procedures used with children.

CONCLUSIONS AND RECOMMENDATIONS

Growth and development issues are significant concerns for clinicians who care for children, including children who have been treated with implants or other medical devices and associated procedures that have the

potential to affect normal growth. The desirable extent and kind of follow-up evaluation of specific medical devices used with children depends on many factors. Among these factors are the characteristics of the device itself, the nature of the intervention as whole (e.g., whether it involves major surgery), the clinical goals for the intervention, the child's disease process and other characteristics (e.g., age, activity, and other underlying conditions), and the depth of supporting knowledge about the device and intervention. Because a pathophysiologic event or anatomic or structural change caused by a complex device may not be evident with a child for a number of years, long-term vigilance is important.

With respect to the effects on implants and other devices of children's active lifestyles and their growth and development, the committee concluded that the systematic consideration of such potential effects should occur during every key stage of device development. Thus, during the conceptualization, development, and preclinical evaluation of a device, manufacturers, FDA staff, and relevant others should ask whether the device may be used with infants, children, or adolescents—and, if so, whether special developmental, growth, activity level, or other issues may be raised by such use that warrant some modification in the design or use of a device.

By the time a device is tested clinically with children (if it is), investigators should have identified certain expected risks and should also be prepared to detect additional unexpected complications. This stage of testing forms a second line of defense against harm to children. Thus, those designing and reviewing clinical trials should consider the significance of growth and development concerns in determining the appropriate length of clinical studies to support the approval of an implant or other relevant device for use with children. They may have to weigh the potential benefits of shorter premarket studies (that allow earlier decisions about approval) against the potential harms of waiting for long-term negative outcomes to be detected after a device is marketed. Depending on the device and other factors, the prospect of longer-term postmarket studies may be considered in the planning of preapproval or preclearance studies. For example, one consideration might be the selection of study sites and investigators (and research participants) who are prepared to continue in a postmarket registry or other study.

Clinician, user facility, manufacturer, and FDA surveillance of device performance after the marketing of a device is a third safeguard for children. Alert and prepared clinicians and provider organizations are the frontline when it comes to identifying apparent device-related problems for reporting as adverse events and for consideration in postmarket evaluations. FDA should be prepared to withdraw approval or clearance, modify device labeling, or otherwise respond if valid follow-up information supports such action.

Because pediatric issues with implants and other medical devices have

not received the same degree of systematic and explicit consideration or analysis that has been devoted to drugs, all parties involved with the initial and continued design and evaluation of medical devices have little formal, evidence-based guidance about differences between children and adults that are relevant for different medical devices. FDA's recent guidance on premarket assessment of pediatric medical devices, which was discussed in Chapter 2, is a step in the right direction as are the document on neurological devices used with children and the earlier guidance on CT scans with children. The usefulness of additional FDA advice or discussion on pediatric questions should be systematically evaluated in a number of areas, potentially including orthopedics, craniofacial fixation devices, and material biocompatibility.

Recommendation 6.1: FDA should develop additional guidance for its own staff as well as for manufacturers and investigators on the identification and evaluation of pediatric questions or concerns at all stages in the design and evaluation of medical devices used with children.

In developing further pediatric guidance, FDA will want to consider the broad range of variables that may affect device safety. Among these are the environment of use (e.g., hospital, home, or school); operator characteristics (e.g., professionals, patients, or family caregivers); complexity of use (and the associated learning curve); patient developmental status (physical, cognitive, emotional); and use of a device for purposes not systematically studied. To oversee the development of such advice and more generally coordinate attention to concerns involving children, FDA should establish a central point of responsibility for pediatric issues within the Center for Devices and Radiological Health (CDRH) as recommended in Chapter 7.

The promotion and expanding use of electronic patient information systems presents opportunities both to improve surveillance of adverse device events (and hazards) and to undertake more systematic studies of device outcomes. However, this chapter and Chapter 4 have noted several limitations in the utility of such databases for the identification (or prevention) of adverse device events and the systematic study of device safety and effectiveness. In particular, the feasible and useful coding of device information in the medical record has presented many complexities, especially for common "generic" devices such as various kinds of tubing.

Despite the complexities, it is essential that FDA and others continue work on a commonly accepted coding system that allows the more precise identification of specific types and models of devices than is possible with existing coding. This kind of work is critical on multiple fronts, including more efficient and valid identification of device exposure and outcomes in automated databases to support clinical studies and active surveillance of clinical care. When combined with progress in device epidemiology as a

field, such work can help fill gaps in knowledge about safety and effectiveness across the range of postmarket uses of medical devices.

Recommendation 6.2: As part of government and private health informatics initiatives, such as those supporting the electronic medical record, FDA should promote the development and adoption of common device coding and other standards and approaches for capturing and linking use and outcomes data for medical devices. FDA should also work with agencies such as the Agency for Healthcare Research and Quality and university- and industry-based methodologists to strengthen methods and tools for epidemiologic research on medical device safety.

FDA and others could also benefit from more comprehensive information about registries and similar resources that would, in some fashion, track pediatric experience with medical devices. Such information could be provided by a "registry of registries" that included not only registries created as part of FDA postmarket surveillance activities but also relevant registries supported by NIH, professional societies, and others. Such a compilation could provide a basis for evaluating registries and developing guidance for improving registries as a basis for long-term device follow up (Peterson et al., 2004). Although details about FDA-required registries and registry-based studies may now be treated by the agency as confidential, more open access to information about postmarket studies in general should be provided, as recommended in Chapter 5.

Recommendation 6.3: As a resource for itself and others, FDA should create or collaborate with others to create a registry of relevant registries, that is, a database with information about registries that are either device specific or that have the potential to provide information useful in evaluating device safety and effectiveness.

For postmarket device safety to become a more significant focus of attention within FDA, it would be helpful for CDRH to have its own extramural research program similar to that administered by the Center for Drug Evaluation and Research. An extramural program could, for example, support studies using external data sources for postmarket research on device safety questions. These data sources include the HMO Network, Medicare and Medicaid databases, National Electronic Injury Surveillance System (see Chapter 4), and the kinds of registries cited in this chapter. An extramural research program could also help advance the field of device epidemiology, which is, as discussed earlier, an underdeveloped area.

Recommendation 6.4: As part of a public commitment to postmarket surveillance of device safety, the Center for Devices and Radiological Health should have its own extramural research program to support studies using external data sources.

As noted earlier in this report, many complex devices are covered by 510(k) procedures that specify clearance rather than approval of devices before marketing. Some clearance decisions cover devices that involve significant changes from their predecessors (predicate devices). FDA can ask for clinical studies prior to clearing devices, although clinical data are submitted for only a small percentage of devices that go through clearance. FDA cannot, however, order postmarket studies as a condition for clearance. It can (but rarely does) order studies subsequent to clearance through its Section 522 authority. Studies that are ordered subsequent to the approval or clearance of a device are limited to 3 years (which often means a shorter period of evaluation for most individual study subjects). This may be too short a period for certain safety problems or developmental effects to be revealed.

Recommendation 6.5: Congress should amend Section 522 of the Federal Food, Drug, and Cosmetic Act to

- **permit FDA to order postmarket studies as a condition of clearance for the categories of devices for which Section 522 Postmarket Surveillance studies are now allowed and**
- **allow FDA to tailor the duration of Section 522 studies of devices likely to have significant pediatric use so that studies can take into account children's growth and development and, if appropriate, exceed the current 3-year limit on study length.**

This recommendation is intended to give FDA more flexibility without prejudging how often the authority would be used. As noted in Chapter 5, the existing Section 522 authority has only been used twice in recent years.

FDA may, of course, encourage long-term studies that it cannot order or is reluctant to order. It can and should work cooperatively with manufacturers to find ways to collect additional, valid information on products that raise concerns about long-term outcomes. It can also encourage pediatric professional societies, academic medical centers, and clinical researchers to get more involved in postmarket device surveillance, for example, by cooperating to create well-designed registries for important medical devices (or device-relevant diagnoses) and undertake registry based-studies that can help answer questions about long-term device effects. FDA can likewise suggest studies for CERTs investigators, including

but not limited to the centers that focus on pediatric topics and medical device questions.

Clearly, many factors influence the long-term safety of medical devices used with children. Scientific and clinical understanding of these factors is limited in many areas, including the underlying biological and physiological phenomena that affect device performance. For example, little is known of the molecular and cellular mechanisms of host-implant interactions that may affect outcomes for pediatric implants and transcutaneous devices. At the behavioral level, strategies that help clinicians, manufacturers, and others communicate successfully with patients and families about the safe and effective use of medical devices at home are little explored.

Given this range of fundamental questions, an opportunity exists for publicly funded national research and research funding organizations to collaborate with industry and FDA to identify priorities for biomedical and bioengineering research to reduce gaps in knowledge about medical device safety and effectiveness. Organizations to involve in such collaboration include not only NIH and AHRQ but also the Centers for Disease Control and Prevention, the National Science Foundation, the Department of Veterans Affairs, the Department of Defense (which operates military health programs), and the National Institute of Standards and Technology.

Recommendation 6.6: FDA should collaborate with the National Institutes of Health, the Agency for Healthcare Research and Quality, and other research funding agencies and interested parties to define a research agenda and priorities for the evaluation of the short- and long-term safety and effectiveness of medical devices used with growing and developing children.

A conference sponsored by funding agencies would be a constructive first step in constructing a research agenda for pediatric device safety and effectiveness. Participants should include researchers and methodologists, engineers, pediatricians and other knowledgeable clinicians, manufacturers, regulators, and representatives of child patients and families. Among the topics considered should be adverse events, including not only catastrophic events but also less dramatic, higher frequency events that may impose significant individual and public health burdens.

Many worthy subjects for further investigation with children can be identified, but resource and feasibility issues inevitably limit what can be done. This committee did not attempt to set priorities for pediatric device research. Some broad objective and subjective criteria can, however, be cited for FDA, NIH, manufacturers, professional societies, and others to consider in targeting topics for investigation. These criteria include

- prevalence among children of a condition treated with a medical device;
- presence of significant developmental questions;
- uncertainty about the short-term or long-term safety and effectiveness of a device to diagnose or treat a condition;
- known or potential burden (mortality, morbidity, impaired functioning, diminished quality of life) on children and their families;
- variability in clinical practice;
- potential of a study to affect clinical practice or regulatory actions; and
- potential relevance of research findings to other medical conditions or devices.

The recommendations presented above clearly require that many, in addition to FDA, share responsibility for the development of better information about the safety and effectiveness of medical devices used with children. This theme of shared responsibility is reiterated and expanded in the next chapter.

7

Children and Medical Device Safety: A Shared Responsibility

"It is critically important that the safety and performance of medical devices are continually assessed when they are in use. . . . No amount of rigour in the pre-marketing review process can predict all possible device failures or incidents arising from device misuse. It is through actual use that unforeseen problems related to safety and performance can occur."
World Health Organization (WHO), 2003, p. 13

As this report was being drafted, studies that identified serious adverse effects of several commonly prescribed medications were attracting widespread news coverage and focusing congressional and public attention on the U.S. Food and Drug Administration's (FDA's) evaluation and monitoring of drug safety (see, e.g., Grassley, 2004; Harris, 2004; Horton, 2004; Vedantam, 2004; Eisenberg, 2005; Okie, 2005). Particular questions were being raised about the timely availability of information to clinicians and the public from postmarket studies of drugs previously approved by the agency. Other questions focused on the independence of FDA assessments and decision making, the balance between premarket and postmarket regulatory programs, and the adequacy of resources for postmarket safety monitoring.

By and large, the public concerns about FDA responsibilities for drug safety have not extended to medical devices. This report has noted that drugs and devices differ in a number of significant ways and that Congress and FDA have reasonably recognized those differences. At the same time, previous chapters of this report have also raised concerns about the limitations of adverse event reporting and analysis and the monitoring of—and public availability of information from—postmarket studies of medical devices. Thus, with respect to certain critical aspects of FDA procedures and performance, differences between drugs and devices are not so acute, and many of the same questions that have been asked about FDA postmarket surveillance of pharmaceuticals can be asked about its surveillance of medi-

cal devices. Furthermore, to the extent that public and professional trust in the FDA is affected by controversy over the agency's monitoring of drug safety, it is appropriate to be concerned about a loss of public confidence in the agency's performance in other arenas.

Much of the discussion in this report pertains to both children and adults because adequate regulatory safeguards for children require an effectively performing basic program for medical device regulation. Upon that foundation, resources and expertise focused on the special needs and characteristics of infants, children, and adolescents should be added. As described in Chapters 1 and 2, Congress recognized this in the Medical Device User Fee and Modernization Act of 2002 (P.L. 107–250), which directed FDA to develop guidance and other resources to strengthen the premarket assessment of medical devices used with children. The Center for Devices and Radiological Health (CDRH) has recently created a pediatric webpage, a useful step to encourage attention to pediatric concerns related to medical devices. Responding to further legislative directives in the Medical Devices Technical Corrections Act of 2004 (P.L. 108–214), the agency solicited views and prepared a report on barriers to and possible incentives for the development of devices to meet children's special needs and characteristics (FDA, 2004y). Box 7.1 summarizes key points in that report.

Other legislation has also directed FDA attention to pediatric issues, mostly related to pharmaceuticals. Among a number of provisions related to children, the Best Pharmaceuticals for Children Act of 2002 (P.L. 107–109) directed FDA to create an Office of Pediatric Therapeutics to be responsible for coordinating and facilitating FDA activities that affect children and the practice of pediatrics. The Office was created in October 2002. The legislation also directed the creation of a Pediatric Advisory Committee to advise the FDA Commissioner on pediatric issues (see, FDA, 2003k). Although pediatric therapeutics includes the use of medical devices, the website for the Office of Pediatric Therapeutics focuses nearly exclusively on drugs.

Beyond the existing CDRH pediatric webpage and guidance documents, FDA should act to organize a central point of knowledge and coordination for pediatric issues within CDRH specifically. That focal point or unit would be responsible for evaluating the adequacy of the Center's access to pediatric expertise and its attention to pediatric issues in all phases of the Center's work, including premarket reviews, postmarket surveillance, device labeling related to pediatric use, and outreach to other public and private organizations and individuals concerned with children's health and well-being. For example, to support families caring for a device-reliant child in the community, the unit could work with the Center's home health committee to develop easier and more accessible adverse event reporting opportunities and more resources on safe device use as recommended in

BOX 7.1
Key Points in FDA Report to Congress on Barriers to the Availability of Medical Devices Intended for the Treatment or Diagnosis of Diseases and Conditions That Affect Children

[N]o commonly accepted definition of "unmet pediatric device need" exists. . . . [W]ithout a clear definition of this term, identifying the needs of pediatric patients cannot be fully accomplished (p. i).

The majority of commenters [responding to the Department's request for comments] representing all groups indicated that the cost of developing pediatric medical devices is the most significant barrier to the development of new pediatric medical devices. The economic challenges noted include not only the limited size of the pediatric device market, but also that the return on the investment required to develop and test pediatric devices usually falls below the profit goals of most medical device companies (p. 12).

[I]t is unknown what the relative contributions are of the small market for pediatric devices, insufficient [health plan] reimbursement, difficulty in obtaining clinical data for FDA approval, and perceived increased liability associated with pediatric devices to the creation of unmet needs in this patient population. In addition, the barriers actually contributing to the existence of unmet needs may not be the same for each device (p. i).

[R]ecommendations for fostering the development and availability of pediatric devices . . . generally fall into the following categories: legislative actions; regulatory actions; funding for research and development; financial incentives; and enhanced information gathering and exchange (p. ii).

[F]urther discussion and study are necessary to evaluate which proposals might be more, or less, effective in addressing the barriers to pediatric device development generally or which proposals might be more, or less, effective in facilitating the development of specific categories of pediatric devices (e.g., for pediatric cardiology) (p. ii).

[I]t is premature to recommend any substantive policy changes, including administrative and legislative changes, at this time. . . . [T]he next step is to conduct a systematic needs assessment to determine the scope of unmet device needs in the pediatric population (p. ii).

SOURCE: FDA, 2004y.

Chapter 4. More generally, the unit could promote partnerships with industry, health care providers, patient advocates, and others to strengthen device surveillance in pediatrics and demonstrate its value in reducing risks to children.

Recommendation 7.1: FDA should establish a central point of responsibility for pediatric issues within the Center for Devices and Radiological Health to evaluate the adequacy of the Center's use of pediatric expertise and its attention to pediatric issues in all aspects of its work.

The remainder of this chapter summarizes what the committee concluded about FDA postmarket surveillance of pediatric medical devices. (A complete list of recommendations is included at the end of the summary in the front of the report.) The discussion recognizes concerns about FDA resources and notes some of the tensions in public policy that complicate FDA's work. The final section emphasizes that assuring the safe design and use of medical devices is a shared responsibility.

FDA PERFORMANCE OF POSTMARKET SURVEILLANCE OF MEDICAL DEVICES

The basic goal of FDA's program of adverse event reporting and postmarket studies for medical devices is to protect patients from harm by identifying and evaluating potential or actual safety problems with legally marketed devices. Appropriate responses to problems in the form of safety alerts or public health notifications and monitoring of device recalls are also part of the postmarket framework to protect patients from unsafe devices as are inspections of device manufacturing sites. These activities should operate in tandem with the agency's premarket activities, which include its guidance to developers and manufacturers on the design and testing of medical devices and its assessment of the safety and effectiveness of devices that require clearance or approval before marketing. The feedback of information from the postmarket unit to the premarket unit within CDRH is a critical step to assure device safety.

Postmarket surveillance, ideally, should promote the early detection of previously unsuspected safety problems as new devices are used with larger and more varied populations and in different circumstances than those evaluated before market approval or clearance. At the same time, it should take a long-term view, supporting investigations or monitoring that can identify problems as devices are used for longer periods than during their initial testing. Surveillance should cover the use of devices in all settings of patient care, including the home.

As undertaken by FDA, postmarket surveillance should be seen as objective, trustworthy, and effective. The program should seek to minimize avoidable constraints on beneficial innovation while also serving as a resource and stimulus for product improvement. The identification of problems with the design or use of medical devices should be understood as a shared responsibility for the clinicians, hospital staff, manufacturer person-

nel, researchers, and others who supply the basic data or undertake the studies necessary to achieve the goals of surveillance.

With respect to the questions posed for the Institute of Medicine (IOM), preceding chapters of this report have noted some shortfalls from adequate performance. As summarized below, these shortfalls, by and large, are not specific to pediatric questions, so responses must be general.

Monitoring of Postmarket Study Commitments

The most obvious deficits in the FDA's program of postmarket surveillance are, first, the lack of effective procedures to monitor the fulfillment of postmarket study commitments and, second, the lack of public information about the status and results of studies ordered by the agency. In the absence of a study monitoring and reporting system, neither the agency nor the committee could reliably identify required postmarket studies (or negotiated voluntary studies) that included pediatric questions. To the extent that premarket approvals of devices identify important follow-up questions that are subsequently ignored, FDA's failure to monitor the status of studies threatens confidence in both premarket and postmarket protections.

As described in Chapter 5, the agency has announced plans to institute systematic monitoring of postmarket study commitments for medical devices, but it has not released specific details. For example, how much information will be available to the public? Will studies involving children be readily identifiable? Will additional resources be available for new monitoring and reporting activities? If the monitoring of postmarket study commitments is simply an addition to the workload of those responsible for evaluating adverse event reports and other postmarket surveillance activities, then progress in monitoring may be offset by reduced performance in other areas.

The agency has until 2007 to submit a required report to Congress on the extent to which companies comply with postmarket study commitments. *The agency should strive to have a monitoring and reporting system in place well before then.* That system should allow searches to identify any studies directed at pediatric populations, and it should also cover voluntary studies negotiated between FDA and manufacturers.

Public Access to Information from Postmarket Studies

Monitoring of postmarket study commitments is important, but so is greater openness about study methods and findings. Although negative study findings may prompt a safety alert and positive findings may prompt publication and promotion of those results, no reliable avenue now exists to disseminate study findings—especially negative information—that may

be of value to clinicians, patients, and families as they make treatment decisions. Furthermore, when information is made public, it can be difficult to assess if details are not also provided about the methods employed to generate it. Such details are particularly important to help clinicians and other knowledgeable intermediaries evaluate reported results and advise patients and families.

Thus, beyond reports on the status of studies, Congress and the agency should provide for more open access to information about required studies, including summaries of findings that take into account the quality of the study's methods and threats to the validity and generalizability of findings. The details of open access will require careful consideration and consultation with researchers, manufacturers, and other interested parties so that the agency does not publicize findings from studies that are badly designed, poorly executed, or inappropriately analyzed. The thinking now being applied to the design of a registry of clinical trials and the operation of an independent drug safety board may produce useful guidelines for such access.

Adequacy of Postmarket Studies

With respect to whether FDA-ordered postmarket surveillance studies last long enough or are adequate to assess the impact on device performance and longevity of children's active lifestyles or their growth and development, the committee lacked sufficient information to identify such studies and answer the questions posed to it. From the information it did locate, the committee expects that many important questions about long-term outcomes remain unstudied. By continuing to direct more attention to pediatric issues related to both medical devices and drugs, Congress will encourage more systematic consideration of long-term safety and effectiveness within and beyond FDA.

FDA's authority to order postmarket studies of medical devices is limited in some important respects. One limitation is that for devices already cleared or approved, the agency cannot order studies to last more than 3 years. For children, some important developmental consequences may not be evident within that period. Another limitation is that the agency cannot order postmarket studies as a condition of its clearance of a device under 510(k) procedures, although it can order such studies after clearance. Just as FDA can and in some instances does ask for clinical data before clearing a medical device, it is reasonable for the agency to have the authority to ask *at the time of clearance* for additional information to be collected after a device is marketed. Thus, as recommended in Chapter 6, Congress should provide FDA with the authority to order postmarket studies as a condition of clearance for those devices for which it can now order Section 522

Postmarket Surveillance. It should likewise authorize studies lasting longer than 3 years if appropriate and reasonable to assess safety and effectiveness with children.

The committee recognizes that requiring more postmarket pediatric studies could, in some cases, prompt a device manufacturer to label a device as not indicated for children rather than risk the extra costs and complications of postmarket studies. Negotiation with manufacturers and consideration of alternatives to required studies may be more constructive in some situations.

The committee also recognizes that most postmarket research does not result from FDA requirements but is undertaken voluntarily by industry, academic, and other researchers. As FDA increases its consideration of pediatric use of medical devices, it should not focus solely on manufacturers to develop more systematic postmarket information on the safety of medical devices used with children. Some studies may be more appropriately sponsored or undertaken by the National Institutes of Health (NIH), the Centers for Education and Research on Therapeutics (CERTs), pediatric professional societies, academic medical centers, and other health care or research organizations. Agency advisory committees may want to consider directing some suggestions for further study to these groups. As noted in Chapter 6, the Agency for Healthcare Research and Quality (AHRQ) recently announced that it planned to fund a new CERT that would focus on medical devices.

CDRH should also be provided with resources for its own program of extramural research. In addition, as recommended in Chapter 6, FDA should collaborate with NIH and others to develop a research agenda and priorities for postmarket studies—especially long-term studies—of devices with substantial pediatric use. Given that there is no shortage of important questions, Chapter 6 listed some criteria that could be used by FDA and others to set priorities for postmarket studies of medical devices.

Adverse Event Reporting

Judgments about the adequacy of the FDA program of adverse event reporting must take into account the generally recognized problems with such reporting described earlier in the report. Underreporting and incomplete or inaccurate reporting are not confined to this program. In some important respects, substantial progress in detecting, reporting, understanding, and preventing adverse device events and medical errors involving devices will depend less on FDA regulations than on the results of individual and collaborative efforts by hospitals, health plans, professional societies, and others to increase professional and provider accountability for patient safety. Thus, FDA should continue to encourage, monitor, and

participate in adverse event reporting and other patient safety initiatives beyond its own boundaries.

It is essential, however, that FDA continue efforts to strengthen its own spontaneous reporting program for medical devices and its pilot MedSun program. Chapter 4 offered several recommendations for program improvements. It also expressed concern about the adequacy of resources for postmarket device surveillance.

In the MedSun program, the agency has an opportunity to use the participating children's hospitals as connecting points for broader efforts to improve device-related surveillance and problem reporting at the 200 or so children's hospitals and related institutions nationwide. Many of these institutions already cooperate in various safety and quality improvement efforts. Moreover, improved surveillance in these institutions can generate information that may help improve care even in facilities that do not emphasize pediatric services.

FDA and CDRH specifically are uniquely situated to promote attention to events, errors, and design problems related to medical devices. The value-added potential of FDA's device-specific expertise and programs is worth mentioning in several specific areas.

One area is the promotion of more attention to the safety of complex medical devices used in the home and to resources to support patients, families, and other home caregivers in safely operating and maintaining devices and getting timely assistance in resolving problems. Although FDA has created a home care committee, more needs to be done. With responsibility so dispersed compared to hospital care, it will take considerable creativity and commitment to weave a better supporting structure of device safety and surveillance for adults and children cared for outside of medical facilities.

Another important value-added area for FDA, as recommended in Chapter 6, is further promotion of common standards and approaches to capturing data about medical device safety and effectiveness from large automated patient care databases. One priority here is continued work on a commonly accepted coding system that will allow more precise identification of specific types and models of devices than is possible with existing coding. Improved coding will strengthen multiple facets of postmarket surveillance.

Although its work focuses on device safety in the United States, FDA also participates in international efforts to harmonize regulatory policies, share reports on serious device problems in a timely fashion, and promote effective manufacturing facility inspection and other programs to assure device safety in global markets. One area of concern is confidentiality policies or practices in other countries that may impede the timely sharing of critical public health information.

Additional or Independent Review of Safety Issues for Medical Devices

The IOM committee observed with interest FDA's announcement in February 2005 of the creation of an independent Drug Safety Oversight Board within the agency but outside the Center for Drug Evaluation and Research (CDER). Noting that "[t]he public has spoken and they want more oversight and openness," the Secretary of the Department of Health and Human Services (DHHS) said the new unit would provide "emerging information" to clinicians and patients about the risks and benefits of medicines (FDA, 2005i, unpaged). That is, discussion of potential safety problems would not wait until FDA reached conclusions firm enough to prompt a labeling change, safety alert, or other action. The board would, in addition, oversee CDER's management of high-profile drug safety issues. Members of the board would include experts from FDA and elsewhere in DHHS and other departments, and they would consult with outside experts and patient and consumer representatives. FDA has said it will seek ideas from the public about how it might responsibly disseminate information prior to determinations about regulatory action. Many questions about details remain. One important issue is whether resources for the Board will be diverted from other activities important to public safety.

Notwithstanding certain differences between drugs and devices, the basic criteria for evaluating information and responsibly making emerging drug safety information public should—if sound in content and application—apply in broad outline to similar information involving medical devices. As the drug safety board begins to function, the relevance to devices of lessons learned with the new program should also be considered.

At this point, it is not clear that the independent board approach—that is, a unit separated from the relevant FDA center—makes sense for medical devices, although it may. More than is the case for drugs, administrative separation could limit the extent to which information gained in postmarket surveillance of devices feeds back into premarket evaluations and other activities and vice versa. It may also be considerably more difficult for devices than for drugs to draw adequate clinical and technical expertise from various government agencies to help support a separate unit. Finally, if postmarket safety oversight for both devices and drugs were to be combined in a single separate board, the committee is concerned about the potential for device safety to be subordinated to drug safety and for differences between devices and drugs to be ignored.

The committee also notes that the charter of an existing FDA group, the Drug Safety and Risk Management (DSaRM) Advisory Committee, mentions the possibility of the group acting as a medical device panel and, in that event, adding nonvoting representatives of consumer and industry

interests (FDA, 2004d).[1] The DSaRM committee now includes members with expertise in risk perception, risk management, clinical pharmacology, clinical research, pharmacoepidemiology, and medication errors. Differences between drugs and devices and the lack of device-specific expertise on the DSaRM group suggest that it is not properly constituted to consider specific issues related to medical device safety and that simply adding representatives of consumer and industry interests would not rectify that deficit. (Through early 2005, all meetings of the group appear to have involved drugs only.)

RESOURCES TO SUPPORT POSTMARKET DEVICE SURVEILLANCE

The IOM was not charged with evaluating the funding and staffing of CDRH. Still, in examining the adequacy of FDA postmarket surveillance, it is difficult to avoid questions about whether the pressure for speedier approval and clearance of devices has led to an imbalance in resources for premarket and postmarket activities. This pressure is evident in the user fee legislation described in Chapter 3 and in the CDRH 2000–2005 strategic plan, which sets specific goals for reducing the time for device approvals (see, e.g., FDA, 2003f).

In its performance plan for FY 2004, CDRH stated that "recent improvements in review time have been achieved by diverting significant resources from other FDA programs" (FDA, 2003n, unpaged). The performance plan also explicitly characterized several areas within CDRH as "not working well." These areas included postmarket surveillance of medical devices, inspection of device manufacturers, and radiation safety. (The plan characterized the mammography quality standards program as "working well" and the device review and regulatory science programs as "working but facing challenges.")

Because clear numerical benchmarks exist, the most obvious shortfall in performance involves FDA's statutory requirement to inspect facilities that manufacture Class II and III devices every 2 years (21 USC 360(h)).

[1]This committee advises the FDA Commissioner on "risk management, risk communication, and quantitative evaluation of spontaneous reports for drugs for human use and for any other product for which the Food and Drug Administration has regulatory responsibility. The Committee also advises the Commissioner of Food and Drugs regarding the scientific and medical evaluation of all information gathered by the Department of Health and Human Services and the Department of Justice with regard to safety, efficacy, and abuse potential of drugs or other substances, and recommends actions to be taken by the Department of Health and Human Services with regard to the marketing, investigation, and control of such drugs or other substances" (FDA, 2004d, unpaged).

Instead of inspecting half of such facilities each year, the percentage—and even the expressed goal of the agency—has been less than 25 percent (excluding inspections under the new program allowing accredited outside entities or persons to conduct certain inspections) (FDA, 2003n, 2004t). (The inspection requirements apply to an increasing number of device firms, approximately 13,700 in 2001 compared to 9,000 in 1997 [FDA, 2003n]). The FY 2004 performance plan noted that the 1997 legislation (FDA Modernization Act) had reduced the role of premarket review for many low- and medium-risk devices and, in theory, increased reliance on postmarket quality systems, a reliance not supported by resources for monitoring manufacturer performance. The plan also reported high rates of violations in past years.

Others have expressed concern about FDA resources. In 2001, an external review of the role of science at CDRH suggested that the Center's scientific infrastructure may be "eroding in areas such as information systems, laboratory equipment, and training" (FDA, 2001l, unpaged). It particularly stressed concerns that the work of the FDA across the life cycle of medical devices was least attentive to ". . . the feedback loop from postmarket review of one device to pre-market design of its successor. This segment of the cycle is most heavily dependent on recording present experience and passing that on to the next generation of designers (and reviewers/evaluators). In this regard, it was noted by staff that there is no general catalogue or electronic database of decisions reached, or the basis for them, so that undue weight is placed on individual people remembering what happened in some earlier, related situation."

Improvements in information technology and information systems in use at FDA should improve the efficiency of agency operations and make information—for example, the status of postmarket studies—more widely and easily available to those who need it. Such improvements cannot, however, replace the application of substantive knowledge and judgment by a sufficient complement of staff with appropriate clinical, engineering, statistical, and other expertise. Likewise, advance guidance on FDA expectations of device developers and manufacturers can reduce the burden on FDA staff to catch and require correction of deficiencies in these processes, but they do not substitute for on-site inspections that include investigation of complaint handling and adverse event analysis and reporting.

In the Medical Device User Fee and Modernization Act of 2002, Congress authorized additional appropriations for postmarket surveillance activities—$3 million for FY 2003, $6 million for FY 2004, and "such sums as may be necessary" in subsequent years. After this endorsement of the agency's need for additional resources, Congress did not, however, appropriate the additional funds (personal communication, Thomas P. Gross, M.D., Director, Division of Postmarket Surveillance, CDRH, March 28,

2005). The legislation also provided for an FDA report to Congress by January 2007 on the impact of user fees on postmarket device surveillance and the improvements and funding that may be needed for an adequate program.

TENSIONS IN PUBLIC POLICY AND DEVICE INNOVATION

Through statutes and regulations, FDA is charged with simultaneously safeguarding the public and encouraging timely access to safe and effective products. Tensions sometimes exist between these two broad roles of FDA, as suggested at several points in this report. Tension may also exist between the public's desire for governments to protect them from an array of threats to their health and safety and the public's willingness to pay for such protection.

Trade secret and confidentiality provisions related to studies of medical devices and other FDA-regulated products may create tensions between the desire to encourage product innovation and economic growth by allowing innovators and manufacturers to hold certain information secret and the desire to provide clinicians, patients, and others with information that may help them make knowledgeable choices. Given the scarcity of information about the safety and effectiveness of medical devices used with children, this report has argued for greater openness and availability of findings from device studies required by FDA.

Efforts to apply or strengthen safety regulations have the potential to discourage certain innovations. Regulations may add to administrative, testing, or production costs to the point that developers or manufacturers may consider development or marketing of a device economically unattractive. As noted in Chapter 1, the device industry is quite diverse compared to the pharmaceutical industry and includes a larger proportion of small firms. Some of these small companies may struggle with the many facets of medical product regulation, including special requirements for testing medical products with children. Regulations may also create uncertainty among investors about the future of a device, including whether it will be approved for marketing. For example, required reports by publicly held companies often include statements about risks or uncertainties related to clinical trials that are being undertaken to obtain FDA clearance or approval of a device.

For products that are developed primarily for adults and that have a relatively small pediatric market, the regulatory, ethical, practical, financial, and other added costs or challenges of testing a product with children and securing market approval may deter manufacturers from proceeding—especially if existing approval of the device has not restricted use with children. (As described in Chapter 6, special regulatory protections for children involved in research can impede certain kinds of research [IOM,

2004a].) Without systematic testing either before or after marketing, however, problems with pediatric uses of devices may be detected slowly and unsystematically. Then, if questions arise about unlabeled use of a device with children and the absence of pediatric studies, a manufacturer may choose to label a device as not indicated for use with children rather than undertake pediatric testing. This may limit children's access to beneficial devices and increase the potential liability of health care professionals and providers.

The potential for regulations to create unanticipated and unwanted outcomes—such as discouraging beneficial innovation or limiting the information available to guide clinical decision making—makes it important for policymakers to consider the effects of policies on different relevant parties, with attention to the incentives that shape their behavior. Consistent with the protection of patient safety, policymakers should encourage an alignment of incentives and interests among manufacturers, professionals, providers, patients, and regulators that favors cooperation and shared responsibility over blame or conflict.

SHARED RESPONSIBILITIES FOR MEDICAL DEVICE SAFETY

Context: Shared Responsibilities for Patient Safety

FDA programs to protect public health operate within a broader system of shared responsibilities for patient safety and health care quality. In the past two decades, individual and collaborative initiatives to improve the quality of health care and protect patients from harm have grown remarkably and been the subject of many reports (see, e.g., IOM, 1990, 1992, 2000c, 2003, 2004b; AHRQ, 2001, 2003, 2004). A number of these initiatives are sponsored or supported by government agencies, including the various units of DHHS, the Department of Defense (which manages a large military health care system), and the Veterans Health Administration. Other patient safety activities have been sponsored by a growing number of state governments, private-sector coalitions of many kinds and sponsorship, health care accrediting organizations, consumer groups, and health professional societies.

In addition, hospitals and other health care institutions have acted individually as well as in collaboration with others to improve their own systems and promote change in larger systems within which they operate. Health professions educators also contribute to patient safety when they teach—and demonstrate by example—the importance of professional vigilance, including the prevention, recognition, and investigation of device adverse events. This diversity of involvement reflects not only the broad

concern about health care quality and patient safety but also the range of parties whose participation is necessary to improve health care outcomes.

Patient safety initiatives often emphasize drug safety or otherwise do not highlight quality or safety issues that primarily involve medical devices. The focus on medications reflects analyses of medical errors in which medication mishaps figure prominently, although some of these mishaps also involve errors in device use or shortcomings in device design as described in Chapter 4. Like most patient safety initiatives, those focusing on children also tend not to feature medical devices.

Nonetheless, even initiatives that focus narrowly on medication safety or other topics may still encourage practices, procedures, and ways of thinking that can—indirectly or directly—help create an environment that promotes medical device safety. For example, organizational steps to improve team functioning, adherence to medication protocols or guidelines, accuracy in the recording of medication information, and patient and family education can have broader potential benefits. Likewise, efforts to improve the analysis of medication errors through root cause analysis should create skills and concepts that can be applied to other products or processes. In addition, certain specific actions to improve medication safety may at the same time improve medical device safety. Examples include training in the proper use of infusion pumps and redesign of these pumps to reduce opportunities for use errors.

Beyond appreciating these spillover effects, those concerned about the safe design and use of medical devices should examine quality of care and patient safety initiatives and consider how they might be adjusted or expanded to include devices. For example, as procedures to improve tracking and responses to drug safety alerts and recalls are instituted, the need for corresponding procedures tailored to the institutional intake, distribution, and day-to-day use of medical devices should also be evaluated.

Recommendation 7.2: All those engaged in improving the quality of health care and protecting patients from harm should evaluate and sharpen as appropriate their attention to medical device safety, including safety issues that particularly affect children.

As an example of how organizations might expand their focus on medical devices, the committee looked at a set of 20 tips for families to prevent medical errors with children that were developed by the Agency for Healthcare Research and Quality (AHRQ, 2002). Eight of the 20 tips involved medications, for example, "If you have any questions about the directions on your child's medicine labels, ask." Only one question (which recommended asking about the best device for measuring a child's liquid medicine) dealt with a device. Some questions could have been modified to include medical devices, and device-specific questions could have been added. Examples of

such questions (some of which draw on items in FDA's home health checklist (FDA, 2003l) described in Chapter 4) include the following.

- Ask for written information, videotape, DVD, or Internet resources on how to safely operate your child's medical device, what to avoid doing, how to recognize and troubleshoot problems, and when and where to seek assistance.
- If you have any questions about your child's medical device, ask your doctor.
- Make sure that you have the name of the device, the model and serial numbers, the manufacturer's name, and contact information.
- Be sure your child's doctors know that the child has an implant and relevant information is clearly recorded in your child's medical record in the event that neither you nor your child's physician is available to provide this information in an emergency.
- Keep in touch with the surgeons or other clinicians involved in implanting a device or otherwise treating your child with a device, so they can find you if they become aware of safety concerns with the device or associated treatment.
- If the manufacturer of your child's implant has asked you to do so, inform them of your new address when you move.

Medical Device Safety

The sharing of responsibilities for making safe medical devices available for use with children extends throughout the medical device product cycle depicted in Chapter 1. That is, it covers both premarket and postmarket activities and the interaction between the two. Rather than identify roles and responsibilities by categories of individuals and organizations, the discussion below is organized by broad stage in this cycle.

Shared Responsibilities: Medical Device Innovation

As discussed in Chapter 6, a first line of safeguards for children begins with those who conceive of and develop high-risk medical devices. From the earliest stage of device development, including the design of prototype devices, engineers, clinicians, and others involved should systematically consider the potential harms as well as potential benefits of a device. Such consideration should include the possible use of a device with children.

FDA contributes at this stage by providing general or specialized guidance to help innovators understand from the outset what is necessary to secure FDA approval or clearance of certain kinds of medical devices. FDA's recent guidance on premarket assessment of pediatric medical de-

vices is a helpful step, but further work is needed to identify and clarify characteristics of children that may affect particular aspects of performance and safety for different types of devices.

When possible and especially for devices used at home, designing devices to avoid hazards and harms is preferable to relying on professional and consumer instructions, education, and other steps that may be less effective at preventing problems (Arcarese, 2002b). The FDA human factors initiative has provided guidance to device developers on ways to identify and avoid hazards related to medical device use as part of a larger program of risk management (FDA, 2000b).

When problems do arise with existing devices, feedback from users can be an important source of inspiration or direction for the modification of such devices and the development of new devices. Users include health care professionals and patients or families, but risk managers and others in health care facilities may also provide important insights into a device's strengths and limitations. Many companies have active surveillance programs that support and encourage this feedback of information through multiple means, including field representatives. The yield from these programs—both to manage problems with existing devices and to get direction for refinements and innovations—depends to a considerable extent on whether health professionals and, sometimes, consumers, are aware of their reporting options and are able and willing to use them.

Shared Responsibilities: Systematic Clinical Evaluation of Medical Devices

Beyond the initial stages of conceptualization and development, the systematic evaluation of medical devices, which includes preclinical and clinical testing of higher-risk devices, provides another important set of safeguards for children and another area of shared responsibilities. In addition to tracking hypothesized outcomes with innovative devices, clinical studies identify and evaluate unanticipated adverse events and thereby build the evidence base for device labeling and, subsequently, patient care. FDA has promoted early meetings with device developers to discuss testing and evaluation strategies that will satisfy its standards of evidence when approval is sought to market the device or add new indications for an already approved device. When manufacturers undertake postmarket studies directed by the FDA, they also seek approval of the study plan.

As it regulates and guides the evaluation of medical devices, FDA operates as part of a substantial research infrastructure in the United States that assigns varying degrees of responsibility for overseeing the scientific and ethical soundness of clinical research to a range of parties. Besides FDA, these parties include NIH and other research sponsors, research institutions

such as academic medical centers, and the Institutional Review Boards (IRBs) that review proposed human research for conformity with federal and institutional research protection policies, including special protections for children. FDA has provided guidance for IRBs and others about certain special aspects of device research (e.g., different requirements for "significant risk" devices versus "nonsignificant risk" devices).

This report has outlined some of the challenges involved both in conducting research with children and in conducting clinical studies of medical devices. The latter may involve testing practices that are different from those normally demanded for investigational drugs, for example, the routine use of randomized clinical trials. As a result of such differences, threats to valid research conclusions that may be controllable in drug trials may not be controllable in device studies. This potentially makes the process for evaluating devices before market approval less powerful and increases the burden on postmarket surveillance.

The world of medical device development and evaluation is diverse. It includes companies with focused teams of scientists, engineers, and clinical experts who are backed by significant organizational, financial, management, and other resources to support the translation of new ideas into safe, effective, and profitable products. It also includes smaller firms with more limited resources and, perhaps, more need for guidance from FDA. Less obvious is the role of clinical innovators who are seeking better ways to treat their patients' medical problems and who may operate independently without appreciating that they share responsibility for systematic evaluation of medical interventions.

Although established medical device companies may be able to improve their clinical evaluation procedures, the individual clinical innovator is a weaker link in the process of testing new interventions for safety and effectiveness. New surgical procedures involving medical devices and modifications of medical devices can escape systematic assessment, despite calls for such innovations to be brought into the system of clinical evaluation and human research protections (see, e.g., Solomon and McLeod, 1995; Moss et al., 2001; Ehrlich et al., 2002; McKneally and Daar, 2003; Dent et al., 2004). Manufacturers may be concerned about certain kinds of device modifications that occur outside their infrastructure for testing, evaluation, and follow-up.

Trying to distinguish between progressive, acceptable clinical practice and unscientific and possibly unethical research on humans has proved difficult for the clinical community, research ethics organizations, FDA, and others concerned about the evidence base for clinical care and the ethical conduct of human research. Much of the difficulty in making distinctions stems from the complexities of patient care, especially care for high-risk children who are not being helped by standard practices and for whom specifically appropriate medical devices are not available. Despite

the frustrations and complexity of the task, efforts should continue to evaluate the safety and effectiveness of surgical and device innovation in clinical practice.

Shared Responsibilities: Acting on and Disseminating Findings of Device Studies

For Class III and certain Class II devices, FDA clearly has responsibility for evaluating clinical data and deciding whether it is sufficient to warrant the approval or clearance of a medical device so that a device can be legally marketed. For devices that have gone through the approval process, the agency makes public summaries of the evidence of safety and effectiveness (or safety and probable benefit). It generally does not make public any information about postmarket studies unless their findings prompt a recall, change in labeling, or public health notification. Companies may, however, promote positive study findings from such studies through press releases and other means, including journal publications.

FDA regulates the label and labeling of devices, which may include information based on study findings. Labeling is broadly defined to include promotional materials. (FDA can also regulate the advertising of "restricted devices," i.e., devices whose sale, distribution, or use is restricted by an approval order or by regulation.) The FDA has provided extensive guidance to manufacturers on various aspects of labeling, including the development of information for lay users of home medical equipment (FDA, 1993b).

Within these boundaries, manufacturers have the opportunity and responsibility to provide understandable information and education on the safe and effective use of devices available to clinicians, patients and families, and others who need it. Clearly, the extent and type of information and educational support will vary depending on the complexity of a device and its risks. Professional societies also share responsibility for providing information and evidence-based guidance for clinicians and, in some cases, patients and families.

As described in Chapter 3, FDA operates within a set of statutory restrictions and traditions that have limited the sharing of information about findings of device studies, especially studies conducted following initial approval or clearance of a product for marketing. This report has argued for less secrecy and more openness in the sharing of information related to the potential benefits and harms of medical devices.

Shared Responsibilities: Safety in Device Manufacturing and Supply

Manufacturers must devise and sustain production processes that reliably produce safe products consistent with design specifications and appli-

cable public policies. The vast majority of medical devices are manufactured without defects, but each year sees some device recalls stemming from serious aberrations in manufacturing or packaging processes. These aberrations affect both complex devices and simple devices that normally present low risk to patients. Making devices safely available also requires the participation of distributors, vendors, user facilities, and others who have custody of the devices prior to their use with patients.

FDA provides extensive guidance on manufacturing processes and quality systems for medical products. It also has a system for inspections of manufacturing sites. As noted above, that inspection system has fallen substantially below statutory requirements for frequency of inspections in recent years. Although the reliable and consistent production of safe devices ultimately depends on the integrity and competence of the manufacturer, shortfalls in the FDA inspection program mean that some problems and opportunities for improvement are almost certainly not being identified.

Shared Responsibilities: Safe Use of Safe Medical Devices

Whereas manufacturers have the lead responsibility for the safe manufacturing of effective medical devices that are designed to minimize opportunities for unsafe use, health care professionals and providers have lead responsibility for the safe and appropriate use of devices. The emphasis in discussions throughout this report has been on institutional environments that help health care professionals and others do what they are supposed to do correctly and consistently. Still, individuals within these systems must understand and welcome their personal responsibilities to acquire and apply the knowledge and skills—including communication and other interpersonal skills—needed for safe patient care.

Initial and continuing education is an essential element in preparing physicians, nurses, and other health care professionals to use conventional and innovative medical devices safely and appropriately and to recognize device problems that should be reported. Beyond the education provided by health professions schools, health care facilities, and professional societies, manufacturers of complex devices must also provide or support proper training and assessment for clinicians. This is especially important for innovative products that require new procedures or skills. Simulation strategies may prove particularly helpful for complex devices and procedures that require unusual or particularly difficult skills and techniques.

Familiar devices and familiar safety problems also warrant public and private attention. An example of such attention involves the well-recognized threat of fire when certain devices such as defibrillators are used in oxygen-rich environments. In a 1994 publication, ECRI (a private technology assessment and research organization that has produced a number of fire

safety statements) observed that the danger of fire "during defibrillation has been forgotten or ignored—or was never learned—and must be periodically reemphasized" (ECRI, 1994, p. 307). In 2002, the American Heart Association amended its pediatric life support recommendations. Instead of a 3-step chant to insure people are clear of a patient before an electric shock, hospital personnel are now advised to use a 4-step chant to emphasize the danger of oxygen. Specifically: "I'm going to shock on the count of four. One—I'm clear. Two—you're clear. Three—oxygen's clear. Four—everybody's clear" (Hazinski et al., 2002; cited in Theodorou et al., 2003). Other fire safety initiatives include a safety alert issued by the Joint Commission on the Accreditation of Healthcare Organizations as part of its sentinel event program (JCAHO, 2003).

The responsibility of patients and families for the safe use of medical devices is a more sensitive topic. Families whose children are reliant on complex medical equipment in the home are often under exceptional stress—emotionally, physically, cognitively, and financially. Unless they are fortunate enough to have excellent health insurance or substantial financial resources, they typically lack adequate 24-hour support from trained personnel to operate, maintain, and troubleshoot complicated, life-sustaining equipment. Some children's hospitals and other institutions devote considerable resources to training parents in the use of equipment, evaluating home health agencies and vendors, checking the initial use of equipment in the home, and following up periodically on adherence to care instructions (Mast, 2004; Simpser, 2004). Likewise, some manufacturers have good consumer support programs. In general, however, much more can be done by primary care and specialist physicians, hospitals, home care providers, manufacturers, and FDA to help patients and families meet their responsibilities for using medical devices safely.

Shared Responsibilities: Postmarket Surveillance and Evaluation of Long-Term Safety and Effectiveness

Reflecting its charge, this report has focused primarily on FDA's responsibilities for postmarket surveillance of medical devices, including devices used with children. The discussion of adverse event reporting made clear, however, that health care professionals and health care providers (user facilities) have critical responsibilities for initially detecting, documenting, investigating, and reporting adverse device events—and for putting in place procedures and practices to prevent such events. Manufacturers are crucial in investigating possible device failures and malfunctions to uncover the nature of the problem—which might be intrinsic to the device or could relate to the way it was used—and respond as appropriate. In addition, as described in Chapter 4, various other public and private orga-

nizations and collaborations include some form of adverse event reporting as part of programs to improve the quality of health care and protect patient safety. Some of these efforts involve children's hospitals and pediatric professionals.

Just as reporting and responding to adverse events is a distributed responsibility, so is the systematic study of the safety and effectiveness of marketed devices used with children. In addition to postmarket studies ordered by FDA or undertaken voluntarily by manufacturers, NIH, the CERTs overseen by AHRQ, private foundations, pediatric professional societies, and other groups interested in child health should promote and support safety and effectiveness studies and the databases (e.g., registries) needed to support such studies. The involvement of patient, family, and consumer groups is particularly important for devising strategies to adapt device surveillance to the difficult realities of identifying, understanding, and preventing adverse events with devices used at home and in the community.

To support both adverse event reporting and systematic studies, FDA has been exploring how to use developing statistical tools and exploit large automated patient care databases to identify, understand, and prevent problems with the use or design of medical devices. As discussed in Chapters 4 and 6, initial results have been less promising than hoped, partly because patient records often do not contain information that identifies individual medical devices. Creating feasible coding systems and procedures for including such information has, however, proved daunting. Recommendations in Chapter 6 focus on steps to improve the usefulness of electronic patient records for device surveillance and strengthen FDA research capacity. In any case, university-based and other biostatisticians and epidemiologists can contribute by helping, first, to improve and apply the methods for formal clinical studies of medical devices and, second, to refine the tools for detecting and analyzing adverse events in large databases and developing the field of medical device surveillance.

Notwithstanding the responsibilities and essential contributions of other parties, FDA has an unparalleled combination of authority and expertise to promote more comprehensive, efficient, and effective medical device surveillance. It must use its position both to strengthen its own programs and to encourage others to recognize and meet their shared responsibilities for identifying, understanding, and preventing problems with the design, evaluation, manufacture, maintenance, and use of medical devices. As stressed throughout this report, successful programs of postmarket surveillance to protect all those whose health depends on safe and effective medical devices are an essential foundation for efforts to protect children in particular.

References

AAO (American Association of Orthodontists). 1975. AAO issues special bulletin on extra oral appliance care, Editorial. *American Journal of Orthodontics and Dentofacial Orthopedics* 68:457.

AAP (American Academy of Pediatrics). 1977. Guidelines for the ethical conduct of studies to evaluate drugs in pediatric populations. *Pediatrics* 60(1):91–101.

AAP. 1995. Guidelines for the ethical conduct of studies to evaluate drugs in pediatric populations. *Pediatrics* 95(2):286–294.

AAP. 2000a. Policy statement: Use of inhaled nitric oxide. *Pediatrics* 106(2):344–345.

AAP. 2000b. *Summary Statement by the American Academy of Pediatrics*. Summit: Setting a Research Agenda for Patient Safety, Washington, DC. Agency for Healthcare Research and Quality. [Online]. Available: http://www.aap.org/advocacy/washing/patientsafety.htm [accessed July 8, 2005].

AAP. 2003. Technical report: Pediatric exposure and potential toxicity of phthalate plasticizers. *Pediatrics* 111(6):1467–1474.

AAP, APA (Ambulatory Pediatric Association), APS (American Pediatric Society), AMSPDC (Association of Medical School Pediatric Department Chairs), SPR (Society for Pediatric Research). 2004a (August 20). Letter to Food and Drug Administration re: Response to FDA's Request for Comments on the Availability of Appropriately Designed and Adequately Studied Medical Devices. [Online]. Available: http://www.fda.gov/ohrms/dockets/dailys/04/aug04/082504/04n-0254-c00012-vol1.pdf [accessed July 8, 2005].

AAP, APA, APS, AMSPDC, SPR. 2004b. Statement for the Committee on Postmarket Surveillance of Pediatric Medical Devices, Washington, DC. Institute of Medicine.

Abrams S, Peart I. 1995. Twiddler's syndrome in children: An unusual cause of pacemaker failure. *British Heart Journal* 73(2):190–192.

ACC (American College of Cardiology). 2004. Statement for the Committee on Postmarket Surveillance of Pediatric Medical Devices, Washington, DC. Institute of Medicine.

Acute Care. No date. *Heartstream Patient Analysis System Testing with Pediatric Rhythms*. [Online]. Available: http://www.acutecare.com/pedsaed1.htm [accessed July 8, 2005].

AdvaMed (Advanced Medical Technology Association). 2004. *Inside FDA: A History of the Regulation Process*. Washington, DC: AdvaMed. [Online]. Available: http://www.advamed.org/newsroom/regulatory/fdahistory.pdf [accessed July 8, 2005].

AHA (American Hospital Association). 2004. *Fast Facts on U.S. Hospitals from AHA Hospital Statistics*. [Online]. Available: http://www.hospitalconnect.com/aha/resource_center/fastfacts/fast_facts_US_hospitals.html [accessed July 8, 2005].

Ahern J. 2001 (January/February). Insulin pump therapy for kids. *Diabetes Self-Management*. Unpaged. [Online]. Available: http://www.diabetesselfmanagement.com/article.cfm?aid=472 [accessed July 8, 2005].

Ahmad A, Gangitano E, Odell R, Doran R, Durand M. 1999. Survival, intracranial lesions, and neurodevelopmental outcome in infants with congenital diaphragmatic hernia treated with extracorporeal membrane oxygenation. *Journal of Perinatology* 19(6 Pt 1):436–440.

Ahmadieh H, Javadi M. 2001. Intra-ocular lens implantation in children. *Current Opinion in Ophthalmology* 12(1):30–34.

AHRQ (Agency for Healthcare Research and Quality). 2001. *Making Health Care Safer: A Critical Analysis of Patient Safety Practices. Summary*. Rockville, MD: AHRQ. [Online]. Available: http://www.ahrq.gov/clinic/ptsafety/summary.htm [accessed July 8, 2005].

AHRQ. 2002. *20 Tips to Help Prevent Medical Errors in Children*. Rockville, MD: AHRQ. [Online]. Available: http://www.ahrq.gov/consumer/20tipkid.pdf [accessed July 8, 2005].

AHRQ. 2003. *AHRQ's Patient Safety Initiative: Building Foundations, Reducing Risk. Interim Report to the Senate Committee on Appropriations*. Rockville, MD: AHRQ. [Online]. Available: http://www.ahrq.gov/qual/pscongrpt/ [accessed July 8, 2005].

AHRQ. 2004. *Closing the Quality Gap: A Critical Analysis of Quality Improvement Strategies. Fact Sheet*. Rockville, MD: AHRQ. [Online]. Available: http://www.ahrq.gov/clinic/epc/qgapfact.htm [accessed July 8, 2005].

Albin R. 2002. Sham surgery controls: Intracerebral grafting of fetal tissue for Parkinson's disease and proposed criteria for use of sham surgery controls. *Journal of Medical Ethics* 28(5):322–325.

Alboliras E, Hijazi Z. 2004. Comparison of costs of intracardiac echocardiography and transesophageal echocardiography in monitoring percutaneous device closure of atrial septal defect in children and adults. *American Journal of Cardiology* 94(5):690–692.

Albright AL, Awaad Y, Muhonen M, Boydston WR, Gilmartin R, Krach LE, Turner M, Zidek KA, Wright E, Swift D, Bloom K. 2004. Performance and complications associated with the Synchromed 10-ml infusion pump for intrathecal baclofen administration in children. *Journal of Neurosurgery: Pediatric* 101(1):64–68.

Alexander M, Cecchin F, Walsh E, Triedman J, Bevilacqua L, Berul C. 2004. Implications of implantable cardioverter defibrillator therapy in congenital heart disease and pediatrics. *Journal of Cardiovascular Electrophysiology* 15(1):72–78.

Alonge L (for the Center for Devices and Radiological Health). 2004 (October 18). Letter re: FDA Public Health Web Notification: Final Update of Information for Physicians on Sub-Acute Thromboses (SAT) and Hypersensitivity Reactions with Use of the Cordis CYPHER Sirolimus-Eluting Coronary Stent. [Online]. Available: http://www.fda.gov/cdrh/safety/cypher3.html [accessed July 8, 2005].

Alonso JE, Slongo T. 2001. Children's fractures. In: Rüedi T, Murphy W, eds. *AO Principles of Fracture Management*. Dübendorf, Switzerland: AO Publishing. Pp. 678–701. [Online]. Available: http://www.aopublishing.org/PFxM/pfxm54upd.pdf [accessed July 8, 2005].

AMA (American Medical Association). 2004a. *AMA Provides Outline for Developing National Clinical Trials Registry*. [Online]. Available: http://www.ama-assn.org/ama/pub/category/13949.html [accessed July 8, 2005].

AMA. 2004b. *AMA Recommends That DHHS Establish a Registry for All U.S. Clinical Trials*. [Online]. Available: http://www.ama-assn.org/ama/pub/category/13934.html [accessed July 8, 2005].

Anderson J, Wood H, Allaire P, Bearnson G, Khanwilkar P. 2000. Computational flow study of the continuous flow ventricular assist device, prototype number 3 blood pump. *Artificial Organs* 24(5):377–385.

Arcarese JS. 2002a. *Medical Devices in the Home Healthcare Community: Report of a Public Conference Held September 12–13, 2002 at the Natcher Auditorium, National Institutes of Health*. Rockville, MD: Food and Drug Administration. [Online] Available: http://www.fda.gov/cdrh/CDRHHHC/091202-report.html [accessed July 8, 2005].

Arcarese JS. 2002b. *Report on Home Use Medical Device Meetings*. Washington, DC: The Food and Drug Law Institute. [Online]. Available: http://www.fda.gov/cdrh/meetings/FDLI-home.html [accessed July 8, 2005].

Arias E, Anderson RN, Kung H, Murphy SL, Kochanek KD. 2003. Deaths: Final data for 2001. In: *National Vital Statistics Report*. Vol. 52. no. 3. Hyattsville, MD: National Center for Health Statistics. Unpaged. [Online]. Available: http://www.cdc.gov/nchs/data/nvsr/nvsr52/nvsr52_03.pdf [accessed July 8, 2005].

ATS (American Thoracic Society). 2003. Statement on the care of the child with chronic lung disease of infancy and childhood. *American Journal of Respiratory and Critical Care Medicine* 168(3):356–396.

ATS. 2004a (August 31). Statement for the Committee on Postmarket Surveillance of Pediatric Medical Devices, Washington, DC. Institute of Medicine.

ATS. 2004b. Written statement to the Committee on Postmarket Surveillance of Pediatric Medical Devices, Washington, DC. Institute of Medicine.

Ault A. 2004. House berates FDA, drug makers. *The Scientist* [Online]. Available: http://www.biomedcentral.com/news/20040910/04/ [accessed July 8, 2005].

Avorn J. 2004. The role of pharmacoepidemiology and pharmacoeconomics in promoting access and stimulating innovation. *Pharmacoeconomics* 22(Suppl 2):81–86.

Bachmann C, Hugo G, Rosenberg G, Deutsch S, Fontaine A, Tarbell J. 2000. Fluid dynamics of a pediatric ventricular assist device. *Artificial Organs* 24(5):362–372.

Bartholomew W, Kwak S, Ring D, Snyder B. 2001. Femoral shaft fractures in children: Comparative biomechanical analysis of a new flexible interlocking nail to current treatment methods. *The Orthopedic Journal at Harvard Medical School* 3:79–82. [Online]. Available: http://www.orthojournalhms.org/html/pdfs/manuscript-08.pdf [accessed July 8, 2005].

Bartlett R. 1985. Esperanza. Presidential address. *Transactions—American Society for Artificial Internal Organs* 31:723–726.

Bartlett R, Roloff D, Custer J, Younger J, Hirschl R. 2000. Extracorporeal life support: The University of Michigan experience. *Journal of the American Medical Association* 283(7):904–908.

Baru JS, Bloom DA, Muraszko K, Koop CE. 2001. John Holter's shunt. *Journal of the American College of Surgeons* 192(1):79–85.

Baskett R, Nanton M, Warren A, Ross D. 2003. Human leukocyte antigen-DR and ABO mismatch are associated with accelerated homograft valve failure in children: Implications for therapeutic interventions. *Journal of Thoracic and Cardiovascular Surgery* 126(1):232–239.

Basse C. 2003 (December 27). He was a mechanic, gifted at saving lives. John W. Holter, who invented a shunt that won worldwide acclaim for helping hydrocephalics, has died. He was 87. *Tampa Bay Times*. Unpaged. [Online]. Available: http://www.sptimes.com/2003/12/27/Tampabay/He_was_a_mechanic__gi.shtml [accessed July 8, 2005].

Beal AC, Co JPT, Dougherty D, Jorsling T, Kam J, Perrin J, Palmer RH. 2004. Quality measures for children's health care. *Pediatrics* 113(1):199–209.

Becker D, Nulsen F. 1968. Control of hydrocephalus by valve-regulated venous shunt: Avoidance of complications in prolonged shunt maintenance. *Journal of Neurosurgery* 28(3): 215–226.

Begg C, Cho M, Eastwood S, Horton R, Moher D, Olkin I, Pitkin R, Rennie D, Schulz K, Simel D, Stroup D. 1996. Improving the quality of reporting of randomized controlled trials. The CONSORT statement. *Journal of the American Medical Association* 276:637–639.

Bessound B, deBaere T, Kuoch V, Descuennes E, Cosset M, Lassau N, Roxhe A. 2003. Experience at a single institution with endovascular treatment of complications caused by implanted central venous access devices in pediatric and adult patients. *American Journal of Roentgenology* 180(2):527–532.

Blevins, K. 2003. *FDA's Use of Negative Publicity as an Enforcement Mechanism: Harvard Law School Third Year Paper*. (Unpublished). [Online]. Available: http://leda.law.harvard.edu/leda/data/567/Blevins.html [accessed July 8, 2005].

Bluck J, Petty JA. 2000 (February 24). NASA computer rocket science helps Debakey heart pump team. *NASA News*. Unpaged. [Online]. Available: http://amesnews.arc.nasa.gov/releases/2000/00_14AR.html [accessed July 8, 2005].

Blum-Hareuveni T, Rehany U, Rumelt S. 2004. Correspondance: Blinding endophthalmitis from orthodontic headgear. *New England Journal of Medicine* 351(26):2774–2775.

Bradlyn AS, Varni JW, Hinds PS. 2003. Appendix C: Assessing health-related quality of life in end-of-life care for children and adolescents. In: Institute of Medicine. *When Children Die: Improving Palliative and End-of-Life Care for Children and Their Families*. Pp. 476–508. Washington, DC: National Academy Press.

Bren L. 2003 (November–December). Company caught in cover-up of medical device malfunctions. *FDA Consumer Magazine*. Unpaged. [Online]. Available: http://www.fda.gov/fdac/departs/2003/603_irs.html [accessed July 8, 2005].

Bright RA. 2004. Panel discussion before the Committee on Postmarket Surveillance of Pediatric Medical Devices, Washington, DC. Institute of Medicine.

Brown S, Bezabeh S, Duggirala H. 2005. *Center for Devices and Radiological Health Condition of Approval Studies As a Postmarket Tool for PMA Approved Cohort 1998–2000*. Rockville, MD: Food and Drug Administration. [Online]. Available: http://www.fda.gov/oc/whitepapers/epi_rep.pdf [accessed July 8, 2005].

Bruley ME. 1994. Accident and forensic investigation. In: van Gruting CWD, ed. *Medical devices: International perspectives on health and safety*. Amsterdam: Elsevier.

Bruno L, Ahrens J. 2005. Examining "operational failures" to reduce home care errors. *Caring* 24(2):34-35.

Cahill A, Baskin K, Kaye R, Fitz C, Towbin R. 2004. Transmural migration of gastrostomy tube retention discs. *Pediatric Radiology* 34(2):143–147.

Campbell A. 2004. Appendix B: State regulation of medical research with children and adolescents: An overview and analysis. In: Institute of Medicine. *Ethical Conduct of Clinical Research Involving Children*. Washington, DC: IOM. Pp. 320–383. [Online]. Available: http://www.nap.edu/books/0309091810/html/ [accessed July 8, 2005].

Campbell R, Smith M, Mayes T, Mangos J, Willey-Courand D, Kose N, Pinero R, Alder M, Duong H, Surber J. 2004. The effect of opening wedge thoracostomy on thoracic insufficiency syndrome associated with fused ribs and congenital scoliosis. *Journal of Bone and Joint Surgery* 86-A(8):1659–1674.

Carstensen PB. 1996. *Overview of FDA's New Human Factors Program Plan: Implications for the Medical Device Industry*. Rockville, MD: FDA. [Online]. Available: http://www.fda.gov/cdrh/humfac/hufacpbc.html [accessed July 8, 2005].

Casey A, Kimmings E, Kleinlugtebeld A, Taylor W, Harkness W, Hayward R. 1997. The long-term outlook for hydrocephalus in childhood. A ten-year cohort study of 155 patients. *Pediatric Neurosurgery* 27(2):63–70.

CDC (Centers for Disease Control and Prevention). 2001. Updated guidelines for evaluating public health surveillance systems: Recommendations from the Guidelines Working Group. *Morbidity and Mortality Weekly Report* 50(RR13):1–35. [Online]. Available: http://www.cdc.gov/mmwr/PDF/rr/rr5013.pdf [accessed July 8, 2005].

Cecchin F, Jorgenson D, Berul C, Perry J, Zimmerman A, Duncan B, Lupinetti F, Snyder D, Lyster T, Rosenthal G, Cross B, Atkins D. 2001. Is arrhythmia detection by automatic external defibrillator accurate for children? Sensitivity and specificity of an automatic external defibrillator algorithm in 696 pediatric arrhythmias. *Circulation* 103(20):2483–2488.

Chalmers T. 1977. Randomize the first patient. *New England Journal of Medicine* 296(2):107.

CHCPR (Center for Home Care Policy and Research). No date. *Working Conditions and Adverse Events in Home Health Care*. [Online]. Available: http://www.vnsny.org/research/projects/1_working.html [accessed July 8, 2005].

Children's Amalgam Trial Study Group. 2003. The children's amalgam trial: Design and methods. *Controlled Clinical Trials* 24(6):795–814.

Clark BC. 1935 (April 2). Senate debate regarding regulation of traffic in food, drugs, and cosmetics. *Congressional Record—Senate* 79:4840–4851.

Clark P, Leaverton P. 1994. Scientific and ethical issues in the use of placebo controls in clinical trials. *Annual Review of Public Health* 15:19–38.

CMS (Centers for Medicaid and Medicare Services). 2004. *Medicare Posts Coverage Decision to Expand Coverage of PET Scans for Alzheimer's Disease*. [Online]. Available: http://www.cms.hhs.gov/media/press/release.asp?Counter=1200 [accessed July 8, 2005].

CMS. No date. *Medicare Coverage—Clinical Trials: Provider Bulletin*. [Online]. Available: http://www.cms.hhs.gov/coverage/8d4.asp [accessed July 8, 2005].

Cochrane D, Kestle J. 2003. The influence of surgical operative experience on the duration of first ventriculoperitoneal shunt function and infection. *Pediatric Neurosurgery* 38(6):295–301.

Coffey R, Edgar T, Francisco G, Graziani V, Meythaler J, Ridgely P, Sadiq S, Turner M. 2002. Abrupt withdrawal from intrathecal baclofen: Recognition and management of a potentially life threatening syndrome. *Archives of Physical Medicine and Rehabilitation* 83(6):735–741.

Cole CH. 2000. Special problems in aerosol delivery: Neonatal and pediatric considerations. *Respiratory Care* 45(6):646–651. [Online]. Available: http://www.aarc.org/marketplace/reference_articles/06.00.0646.pdf [accessed July 8, 2005].

Colin A. 2003. Cystic fibrosis: Diagnosis and treatment. *Pediatric Views* October: Unpaged. [Online]. Available: http://www.childrenshospital.org/views/october03/fibrosis.html [accessed July 8, 2005].

Cordis. 2004. *Press Release: Cordis Announces Nationwide Recall of Revised Instructions for Use for the Precise Rx Biliary Stent Contained in its Medical Device Notification*. [Online]. Available: http://www.cordis.com/active/crdus/en_US/html/cordis/downloads/press/PreciseRX_IFU_Press_Release_050704.pdf [accessed July 8, 2005].

Couldwell W, LeMay D, McComb J. 1996. Experience with use of extended length peritoneal shunt catheters. *Journal of Neurosurgery* 85(3):425–427.

Couzin J. 2004. Drug research: Legislators propose a registry to track clinical trials from start to finish. *Science* 305(5691):1695.

Cronenwett J, Seeger J. 2004. Withdrawal of article by the FDA after objection from Medtronic. *Journal of Vascular Surgery* 40(2):209–210.

Crowley J, Reed, T, Dumais, M. No date. *MDEN - Medical Device Engineering Network*. (Unpublished). [Online]. Available: https://www.medsun.net/participants/uploads/Terrie%20Reed.ppt [accessed July 8, 2005].

Cuka G, Hellbusch L. 1995. Fractures of the peritoneal catheter of cerebrospinal fluid shunts. *Pediatric Neurosurgery* 22(2):101–103.

Cullen D, Bates D, Small S, Cooper J, Nemeskal A, Leape L. 1995. The incident reporting system does not detect adverse events: A problem for quality improvement. *Joint Commission Journal on Quality Improvement* 21(10):541–548.

Curry J, Reeves B, Stringer M. 2003. Randomized controlled trials in pediatric surgery: Could we do better? *Journal of Pediatric Surgery* 38(4):556–559.

Dahan E. 2000. Intraocular lens implantation in children. *Current Opinion in Ophthalmology* 11(1):51–55.

DeAngelis C, Drazen J, Frizelle F, Haug C, Hoey J, Horton R, Kotzin S, Laine C, Marusic A, Overbeke J, Schroeder T, Sox H, Van Der Weyden M. 2004. Clinical Trial Registration: A Statement from the International Committee of Medical Journal Editors. *Journal of the American Medical Association* 292(11):1363–1364.

Dent T, Wortley S, Campbell B. 2004. New interventional procedures. *British Medical Journal* 329(7461):351.

DHHS (Department of Health and Human Services). 1995. Medicare program; criteria and procedures for extending coverage to certain devices and related services. *Federal Register* 60(181):48417–48425.

Dickerman R, Schnieder S. 2002. Recurrent intrathecal baclofen pump catheter leakage: A surgical observation with recommendations. *Journal of Pediatric Surgery* 37(6):E17.

Dickerman R, Stevens Q, Schneider S. 2003. The role of surgical placement and pump orientation in intrathecal pump system failure: A technical report. *Pediatric Neurosurgery* 38:107–109.

Dickersin K, Rennie D. 2003. Registering clinical trials. *Journal of the American Medical Association* 290(4):516–523.

Dickinson JG. 2004a (October). CDRH's Schultz seeks more postmarket reports. *Medical Device & Diagnostic Industry*. Unpaged. [Online]. Available: http://www.devicelink.com/mddi/archive/04/10/008.html [accessed July 8, 2005].

Dickinson JG. 2004b (October). FDA to probe consumer experience with devices. *Medical Device & Diagnostic Industry*. Unpaged. [Online]. Available: http://www.devicelink.com/mddi/archive/04/12/007.html#1 [accessed July 8, 2005].

Dickinson JG. 2004c (August). Regulating the last 25 years: Medical device reporting. *Medical Device and Diagnostic Industry*. Unpaged. [Online]. Available: http://www.devicelink.com/mddi/archive/04/08/007.html [accessed July 8, 2005].

Doctor's Guide. 1996. *FDA Clears New, Thinner Medtronic Drug Pumps for Spasticity and Pain*. [Online]. Available: http://www.pslgroup.com/dg/c736.htm [accessed July 8, 2005].

Dormans J, Criscitiello A, Drummond D, Davidson R. 1995. Complications in children managed with immobilization in a halo vest. *Journal of Bone and Joint Surgery* 77(9):1370–1373.

Doyle D. 2000. Computer programming errors in medicine. *Canadian Journal of Anesthesia* 47(2):188–190.

ECRI. 1993. Hazard: Damaged Allied Healthcare Products Gomco circumcision clamp. *Health Devices* 22(3):154–155.

ECRI. 1994. Fires from defibrillation during oxygen administration. *Health Devices* 23(7): 307–309.

ECRI. 1995. Hazard: Amputations with use of adult-size scissors-type circumcision clamps on infants. *Health Devices* 4(7):286–287.

ECRI. 1997. Hazard: Incompatibility of different brands of Gomco-Type circumcision clamps. *Health Devices* 26(2):76–77.

ECRI. 1999. Hazard: Routine inspection needed for scissors-type circumcision clamps. *Health Devices* 28(3):115–116.

ECRI. 2004a. Elastic nails may promote quicker recovery from pediatric leg fractures. *Health Technology Trends*. Unpaged.

ECRI. 2004b. Fatal air embolism caused by the misconnection of medical device hoses to needleless luer ports on IV administration sets. *Health Devices* 33(6):223–225.

ECRI. 2004c. *Health Devices* 33(12):416–429. [Online]. Available: http://www.ecri.org/marketingdocs/hd331212-toc.pdf [accessed July 8, 2005].

ECRI. 2005. *Medical Device Safety Reports (MDSR). MDSR Document Classifications*. [Online]. Available: http://www.mdsr.ecri.org/information/picklists.aspx [accessed July 8, 2005].

Ehrlich P, Newman K, Haase G, Lobe T, Wiener E, Holcomb G. 2002. Lessons learned from a failed multi-institutional randomized controlled study. *Journal of Pediatric Surgery* 37(3):431–436.

Eisenberg R. 2005. Learning the value of drugs—is Rofecoxib a regulatory success story? *New England Journal of Medicine* 352(13):1285–1287.

Elliot V. 2004 (July 5). Drug controversies prompt call for clinical trial registry. *AMNews.com*. Unpaged. [Online]. Available: http://www.ama-assn.org/amednews/2004/07/05/hll20705.htm [accessed March 3, 2005].

English A, Kenney K. 2003. *State Minor Consent Laws: A Summary*. 2nd ed. Chapel Hill, NC: Center for Adolescent Health & the Law.

Eppley B, Morales L, Wood R, Pensler J, Goldstein J, Havlik R, Habal M, Losken A, Williams J, Burstein F, Rozzelle A, Sadove A. 2004. Resorbable PLLA-PGA plate and screw fixation in pediatric craniofacial surgery: Clinical experience in 1883 patients. *Plastic and Reconstructive Surgery* 114(4):850–856.

EU (European Union). 1990. *Council Directive 90/385/EEC of 20 June 1990 on the Approximation of the Laws of the Member States Relating to Implantable Medical Devices*. Brussels, Belgium: Office for Official Publication of European Communities. [Online]. Available: http://europa.eu.int/smartapi/cgi/sga_doc?smartapi!celexapi!prod!CELEXnumdoc&lg=EN&numdoc=31990L0385&model=guichett [accessed July 8, 2005].

EU. 2003. *Council Directive 93/42/EEC of 14 June 1993 Concerning Medical Devices*. Brussels, Belgium: Office for Official Publication of European Communities. [Online]. Available: http://europa.eu.int/eur-lex/en/consleg/pdf/1993/en_1993L0042_do_001.pdf [accessed July 8, 2005].

Family Practice News. 2000 (June 15). Aspiration of syringe cap. brief article. *Family Practice News*. Unpaged. [Online]. Available: http://www.findarticles.com/p/articles/mi_m0BJI/is_12_30/ai_63922877 [accessed July 8, 2005].

Farrell P, Avery M. 1975. Hyaline membrane disease. *American Review of Respiratory Disease* 111(5):657–688.

FDA (Food and Drug Administration). 1974. Chapter 1. Food and Drug Administration, Department of Health, Education, and Welfare: Public information. *Federal Register* 39(248):44601–44642.

FDA. 1978. Good manufacturing practices for medical devices. *Federal Register* 43:31508.

FDA. 1990. *Device Recalls: A Study of Quality Problems*. Rockville, MD: FDA.

FDA. 1992. New drug, antibiotic, and biological drug product regulations; accelerated approval; Final rule. *Federal Register* 57(239):58942–58960. [Online]. Available: http://www.fda.gov/cder/guidance/append4.pdf [accessed July 8, 2005].

FDA. 1993a. *FDA Safety Alert: Unsafe Patient Lead Wires and Cables*. Rockville, MD: FDA. [Online]. Available: http://www.fda.gov/cdrh/comp/guidance/fod889.pdf [accessed July 8, 2005].

FDA. 1993b. *Write It Right: Recommendations for Developing User Instruction Manuals for Medical Devices Used in Home Health Care*. Rockville, MD: FDA. [Online]. Available: http://www.fda.gov/cdrh/dsma/897.pdf [accessed July 8, 2005].

FDA. 1994. Specific requirements on content and format of labeling for human prescription drugs; revision of "Pediatric Use" subsection in the labeling; final rule. *Federal Register* 59:64240. [Online]. Available: http://www.fda.gov/cder/pediatric/frde1394ped.htm [accessed July 8, 2005].

FDA. 1996a. *FDA Strengthens Standards for New Medical Devices*. [Online]. Available: http://www.fda.gov/bbs/topics/answers/ans00763.html [accessed July 8, 2005].

FDA. 1996b. Medical Devices; Current Good Manufacturing Practice (CGMP) Final Rule; Quality System Regulation. *Federal Register* 61(195):52601–52662. [Online]. Available: http://www.fda.gov/cdrh/humfac/frqsr.html [accessed July 8, 2005].

FDA. 1996c. *Statistical Guidance for Clinical Trials of Non-Diagnostic Medical Devices*. [Online]. Available: http://www.fda.gov/cdrh/ode/ot476.html [accessed July 8, 2005].

FDA. 1997a. Medical devices; establishment of a performance standard for electrode lead wires and patient cables. *Federal Register* 62(90):25477–25498. [Online]. Available: http://www.fda.gov/cdrh/comp/fr0509ap.pdf [accessed July 8, 2005].

FDA. 1997b. *Medical Device Reporting for Manufacturers*. Rockville, MD: FDA. [Online]. Available: http://www.fda.gov/cdrh/manual/mdrman.pdf.

FDA. 1998a. *Annual Report Changes in Tracking and Postmarket Studies Requirements*. [Online]. Available: http://www.fda.gov/cdrh/annual/fy98rpt.html [accessed July 8, 2005].

FDA. 1998b. *Device Advice: Postmarket Surveillance Studies*. [Online]. Available: http://www.fda.gov/cdrh/devadvice/352.html [accessed July 8, 2005].

FDA. 1998c. Dissemination of Information on Unapproved/New Uses for Marketed Drugs, Biologics, and Devices. *Federal Register* 63(224):64555–64588. [Online]. Available: http://www.fda.gov/cdrh/modact/fr112098a.html [accessed July 8, 2005].

FDA. 1998d. *General Controls for Medical Devices*. [Online]. Available: http://www.fda.gov/cdrh/devadvice/363.html#restricted_devices [accessed July 8, 2005].

FDA. 1998e. *Guidance for Industry and FDA Staff: SMDA to FDAMA: Guidance on FDA's Transition Plan for Existing Postmarket Surveillance Protocols*. [Online]. Available: http://www.fda.gov/cdrh/modact/smdatran.html [accessed July 8, 2005].

FDA. 1998f. *Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products*. Rockville, MD: FDA. [Online]. Available: http://www.fda.gov/cder/guidance/1397fnl.pdf [accessed July 8, 2005].

FDA. 1998g. *Guidance for Industry, Review Staff, and the Clinical Community: Guidance on Criteria and Approaches for Postmarket Surveillance*. Rockville, MD: FDA. [Online]. Available: http://www.fda.gov/cdrh/modact/critappr.pdf [accessed July 8, 2005].

FDA. 1998h. *Guidance for Institutional Review Boards and Clinical Investigators—1998 Update: "Off-Label" and Investigational Use of Marketing Drugs, Biologics, and Medical Devices*. [Online]. Available: http://www.fda.gov/oc/ohrt/irbs/offlabel.html [accessed July 8, 2005].

FDA. 1998i. *Guidance on Procedures for Review of Postmarket Surveillance Submissions*. [Online]. Available: http://www.fda.gov/cdrh/modact/postsurv.html [accessed July 8, 2005].

FDA. 1998j. Medical Devices; Exemptions from premarket notification; Class II devices. *Federal Register* 63(13):3142–3145. [Online]. Available: http://www.fda.gov/cdrh/modact/frclass2.html [accessed July 8, 2005].

FDA. 1998k. *New Section 513(f)(2)—Evaluation of Automatic Class III Designation, Guidance for Industry and CDRH Staff*. [Online]. Available: http://www.fda.gov/cdrh/modact/classiii.html [accessed July 8, 2005].

FDA. 1999a. *A Device Clinical Trials Data Bank—Public Health Need and Impact on Industry: A Report to Congress*. Rockville, MD: FDA. [Online]. Available: http://www.fda.gov/cdrh/modact/113(b)main.pdf [accessed July 8, 2005].

FDA. 1999b. *Guide to Inspections of Quality Systems*. [Online]. Available: http://www.fda.gov/ora/inspect_ref/igs/qsit/qsitguide.htm#page47 [accessed July 8, 2005].

FDA. 1999c. Medical Devices; Current Good Manufacturing Practice (CGMP) final rule; Quality system regulation. In: *Medical Device Quality Systems Manual: A Small Entity Compliance Guide,* 1st ed. [Online]. Available: http://www.fda.gov/cdrh/dsma/gmpman.html [accessed July 8, 2005].

FDA. 1999d. Milestones in U.S. food and drug law history. *FDA Backgrounder* [Online]. Available: http://www.fda.gov/opacom/backgrounders/miles.html [accessed July 8, 2005].

FDA. 1999e. *Product Development Protocol*. [Online]. Available: http://www.fda.gov/cdrh/pdp/pdp.html [accessed July 8, 2005].

FDA. 1999f (January 8). *Shunt technology: Challenges and emerging directions*. Conference for the Systematic Technology Assessment of Medicinal Products, Bethesda, MA. FDA. [Online]. Available: http://www.fda.gov/cdrh/stamp/shuntconf.pdf [accessed July 8, 2005].

FDA. 2000a. Draft guidance for infant/child apnea monitor 510(k) submissions; availability. *Federal Register* 65(185):57355–57356. [Online]. Available: http://www.fda.gov/ohrms/dockets/98fr/092200d.htm [accessed July 8, 2005].

FDA. 2000b. *Guidance for Industry and FDA Premarket and Design Control Reviewers: Medical Device Use-Safety: Incorporating Human Factors Engineering into Risk Management*. Rockville, MD: FDA. [Online]. Available: http://www.fda.gov/cdrh/humfac/1497.pdf [accessed July 8, 2005].

FDA. 2000c. *Guidance for Industry: Medical Device Reporting - Alternative Summary Reporting (ASR) Program*. [Online]. Available: http://www.fda.gov/cdrh/osb/guidance/315.html [accessed July 8, 2005].

FDA. 2000d. Medical devices; performance standard for the infant apnea monitor; withdrawal notice. *Federal Register* 65(185):57303–57307. [Online]. Available: http://www.fda.gov/ohrms/dockets/98fr/092200b.htm [accessed July 8, 2005].

FDA. 2000e. *Medical Device Recalls—Class I Recall: Continuous Ventilator (Respirator)*. [Online]. Available: http://www.fda.gov/cdrh/recalls/recall-122200.html [accessed July 8, 2005].

FDA. 2000f. *Note Concerning the March 27, 2000 Amendments to the MDR Regulation to Implement FDAMA Changes*. [Online]. Available: http://www.fda.gov/cdrh/postsurv/note_932700.html [accessed July 8, 2005].

FDA. 2000g. *Safety Notice: Potential for Injury from Circumcision Clamps*. [Online]. Available: http://www.fda.gov/cdrh/safety/circumcision.html [accessed July 8, 2005].

FDA. 2001a. *Appendix B: Alphabetical Patient Codes*. [Online]. Available: http://www.fda.gov/cdrh/mdr/appendixb.pdf [accessed July 8, 2005].

FDA. 2001b. *Appendix C: Numerical Patient and Device Codes*. [Online]. Available: http://www.fda.gov/cdrh/mdr/appendixc.pdf [accessed July 8, 2005].

FDA. 2001c. Draft "guidance for clinical trial sponsors on the establishment and operation of clinical trial data monitoring committees"; Availability. *Federal Register* 66(224):58151–58153. [Online]. Available: http://www.fda.gov/ohrms/dockets/98fr/112001c.htm [accessed July 8, 2005].

FDA. 2001d. *Early Collaboration Meetings under the FDA Modernization Act (FDAMA); Final Guidance for Industry and for CDRH Staff*. [Online]. Available: http://www.fda.gov/cdrh/ode/guidance/310.html [accessed July 8, 2005].

FDA. 2001e. *FDA Clears First External Defibrillator for Use on Young Children*. [Online]. Available: http://www.fda.gov/bbs/topics/ANSWERS/2001/ANS01082.html.

FDA. 2001f. *Guidance for Industry: Postmarketing Safety Reporting for Human Drug and Biological Products Including Vaccines*. Rockville, MD: FDA. [Online]. Available: http://www.fda.gov/cder/guidance/4177dft.pdf [accessed July 8, 2005].

FDA. 2001g. *Guidance on Medical Device Patient Labeling; Final Guidance for Industry and FDA*. [Online]. Available: http://www.fda.gov/cdrh/ohip/guidance/1128.html [accessed July 8, 2005].

FDA. 2001h. Medical devices and radiological health. In: *2002 Performance Plan and Summary*. Rockville, MD: FDA. [Online]. Available: http://www.fda.gov/ope/fy02plan/part2_cdrh.html [accessed July 8, 2005].

FDA. 2001i. *Medical Device Reporting (MDR) (SEE NO. 155)*. [Online]. Available: http://www.fda.gov/cdrh/devadvice/351.html [accessed July 8, 2005].

FDA. 2001j. *MedWatch Medical Device Reporting Code Instructions*. Rockville, MD: FDA. [Online]. Available: http://www.fda.gov/cdrh/mdrcode.pdf [accessed July 8, 2005].

FDA. 2001k. *MRI Safety*. [Online]. Available: http://www.fda.gov/cdrh/safety/mrisafety.html [accessed July 8, 2005].

FDA. 2001l. *Science at Work in CDRH: A Report on the Role of Science in the Regulatory Process*. Rockville, MD: FDA. [Online]. Available: http://www.fda.gov/cdrh/science/science-work-CDRH.html [accessed July 8, 2005].

FDA. 2001m. *Summary minutes*. Meeting of the Circulatory System Devices Advisory Panel Meeting, Gaithersburg, MD. FDA. [Online]. Available: http://www.fda.gov/ohrms/dockets/ac/01/minutes/3766m1.htm [accessed July 8, 2005].

FDA. 2002a. *Avoiding Patient Injuries from Circumcision Clamps*. [Online]. Available: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/psn/printer.cfm?id=92 [accessed July 8, 2005].

FDA. 2002b. *Better Health Care with Quality Medical Devices: FDA on the Cutting Edge of Device Technology*. [Online]. Available: http://intramural.nimh.nih.gov/chp/articles/brain/giedd99c.pdf [accessed July 8, 2005].

FDA. 2002c. *Class II Special Controls Guidance Document: Apnea Monitors; Guidance for Industry and FDA*. [Online]. Available: http://www.fda.gov/cdrh/ode/guidance/1178.html#10 [accessed July 8, 2005].

FDA. 2002d. *Class II Special Controls Guidance Document: Cutaneous Carbon Dioxide ($PcCO_2$) and Oxygen (PcO_2) Monitors; Guidance for Industry and FDA*. [Online]. Available: http://www.fda.gov/cdrh/ode/guidance/1335.html [accessed July 8, 2005].

FDA. 2002e. *Conditions of Approval*. [Online]. Available: http://www.fda.gov/cdrh/devadvice/pma/conditions.html [accessed July 8, 2005].

FDA. 2002f. *Determination of Intended Use for 510(k) Devices; Guidance for CDRH Staff (Update to K98-1)*. Rockville, MD: FDA. [Online]. Available: http://www.fda.gov/cdrh/ode/guidance/857.pdf [accessed July 8, 2005].

FDA. 2002g. *Enforcement Report - November 27, 2002*. [Online]. Available: http://www.fda.gov/bbs/topics/enforce/2002/ENF00771.html [accessed July 8, 2005].

FDA. 2002h. *Guidance for Industry: Information Program on Clinical Trials for Serious or Life-Threatening Diseases and Conditions*. Rockville, MD: FDA. [Online]. Available: http://www.fda.gov/cder/guidance/4856FNL.PDF [accessed July 8, 2005].

FDA. 2002i. *Medical Device Recalls and Corrections and Removals*. [Online]. Available: http://www.fda.gov/cdrh/devadvice/51.html [accessed July 8, 2005].

FDA. 2002j. *Medical Device Recalls—Class 1 Recall: Infant Bassinet*. [Online]. Available: http://www.fda.gov/cdrh/recalls/bassinet032002.html [accessed July 8, 2005].
FDA. 2002k. *Medical Device Recalls: Olympus America Issues Voluntary Recall of Suspect Video Bronchoscopes*. [Online]. Available: http://www.fda.gov/cdrh/recalls/recall-032002.html [accessed July 8, 2005].
FDA. 2002l. *Medical Device Reporting (MDR)—General Information*. [Online]. Available: http://www.fda.gov/cdrh/mdr/mdr-general.html [accessed July 8, 2005].
FDA. 2002m. Medical Devices; Apnea Monitor; Special Controls. *Federal Register* 67(137): 46851–46852. [Online]. Available: http://www.fda.gov/ohrms/dockets/98fr/071702b.htm [accessed July 8, 2005].
FDA. 2002n. *MedSun Medical Product Surveillance Network. Recognition, Investigation and Root Cause Analysis of Medical Device Adverse Events in Healthcare Facilities (Training Materials)*. Rockville, MD: FDA.
FDA. 2002o. Postmarket Surveillance. *Federal Register* 67(109):38878–38892. [Online]. Available: http://www.fda.gov/cber/rules/postsurv.pdf [accessed July 8, 2005].
FDA. 2002p. *Report to Congress: Reports on Postmarketing Studies [FDAMA 130]*. Rockville, MD: FDA. [Online]. Available: http://www.fda.gov/cber/fdama/pstmrktfdama130.htm [accessed July 8, 2005].
FDA. 2002q. *The Least Burdensome Provisions of the FDA Modernization Act of 1997: Concept and Principles; Final Guidance for FDA and Industry*. [Online]. Available: http://www.fda.gov/cdrh/ode/guidance/1332.html#2 [accessed July 8, 2005].
FDA. 2003a. A fond farewell to our readers: Last issue of the user facility reporting bulletin. *User Facility Reporting Bulletin* 37(4):1–2. [Online]. Available: http://www.fda.gov/cdrh/fusenews/ufb42.html#1 [accessed July 8, 2005].
FDA. 2003b. *A Message About HIPAA Compliance for Reporters to FDA MedWatch*. [Online]. Available: http://www.fda.gov/medwatch/hipaa.htm [accessed July 8, 2005].
FDA. 2003c. *Application Methods*. [Online]. Available: http://www.fda.gov/cdrh/devadvice/pma/app_methods.html [accessed July 8, 2005].
FDA. 2003d. *Approval Process*. [Online]. Available: http://www.fda.gov/cdrh/devadvice/ide/approval.shtml [accessed July 8, 2005].
FDA. 2003e. *Early/Expanded Access*. [Online]. Available: http://www.fda.gov/cdrh/devadvice/ide/early.shtml [accessed July 8, 2005].
FDA. 2003f. *FDA Announces New Goal for Reducing Total Device Review Times*. [Online]. Available: http://www.fda.gov/bbs/topics/NEWS/2003/NEW00929.html [accessed July 8, 2005].
FDA. 2003g. FDA's sentinel of public health: Field staff safeguards high standards. *Just the Facts* December:1 [Online]. Available: http://www.fda.gov/opacom/factsheets/justthefacts/7ora.pdf [accessed July 8, 2005].
FDA. 2003h. *Guidance for Industry and FDA Staff: Class II Special Controls Guidance Document: Arrhythmia Detector and Alarm*. Rockville, MD: FDA. [Online]. Available: http://www.fda.gov/cdrh/ode/guidance/1363.pdf [accessed July 8, 2005].
FDA. 2003i. *Guidance for Industry and FDA Staff: Expedited Review of Premarket Submissions for Devices*. [Online]. Available: http://www.fda.gov/cdrh/mdufma/guidance/108.html [accessed July 8, 2005].
FDA. 2003j. *Guidance for Industry and FDA Staff: Medical Device Tracking*. [Online]. Available: http://www.fda.gov/cdrh/comp/guidance/169.html [accessed July 8, 2005].
FDA. 2003k. *Guidance for Industry and FDA Staff: Pediatric Expertise for Advisory Panels*. [Online]. Available: http://www.fda.gov/cdrh/ode/guidance/1208.html [accessed July 8, 2005].

FDA. 2003l. *Home Healthcare Medical Devices: A Checklist*. Rockville, MD: FDA. [Online]. Available: http://www.fda.gov/cdrh/cdrhhhc/brochure-checklist.html [accessed July 8, 2005].

FDA. 2003m. *Home Health Care Medical Devices: Blood Glucose Meters - Getting the Most Out of Your Meter*. Rockville, MD: FDA. [Online]. Available: http://www.fda.gov/cdrh/CDRHHHC/bgm.pdf [accessed July 8, 2005].

FDA. 2003n. Medical devices and radiological health. In: *FY 2004 Annual Performance Plan*. [Online]. Available: http://www.fda.gov/ope/fy04plan/2004pp-cdrh.html.

FDA. 2003o. *Medwatch Reporting Form 3500*. [Online]. Available: http://www.fda.gov/medwatch/safety/3500.pdf [accessed July 8, 2005].

FDA. 2003p. Part 1: Advances in patient care. In: *Office of In Vitro Diagnostic Device Evaluation and Safety's FY 2003 Annual Report*. Rockville, MD: FDA. [Online]. Available: http://www.fda.gov/cdrh/annual/fy2003/ode/part1.html [accessed July 8, 2005].

FDA. 2003q. *Quality System*. [Online]. Available: http://www.fda.gov/cdrh/devadvice/pma/quality_system.html#preapproval [accessed July 8, 2005].

FDA. 2003r. *Quality System Information for Certain Premarket Application Reviews; Guidance for Industry and FDA Staff*. [Online]. Available: http://www.fda.gov/cdrh/comp/guidance/1140.pdf [accessed July 8, 2005].

FDA. 2003s. *What is Human Factors?* [Online]. Available: http://www.fda.gov/cdrh/humanfactors/whatis.html [accessed July 8, 2005].

FDA. 2004a. Agency information collection activities; submission for office of management and budget review; comment request; adverse event pilot program for medical devices. *Federal Register* 69(113):33034–33035. [Online]. Available: http://www.fda.gov/OHRMS/DOCKETS/98fr/04-13211.htm [accessed July 8, 2005].

FDA. 2004b. *Assuring Safe Products in the Market: Postmarket Surveillance: Medical Device Adverse Event Reporting*. [Online]. Available: http://www.fda.gov/cdrh/annual/fy2003/assuring.html [accessed July 8, 2005].

FDA. 2004c. *CDRH Home Health Care Committee (HHCC)*. [Online]. Available: http://www.fda.gov/cdrh/cdrhhhc/index.html [accessed July 8, 2005].

FDA. 2004d. *Committee Charter: Drug Safety and Risk Management Drugs Advisory Committee*. [Online]. Available: http://www.fda.gov/cder/audiences/acspage/DSaRMcharter.htm [accessed July 8, 2005].

FDA. 2004e. Definition of primary mode of action of a combination product. *Federal Register* 69(89):25527–25533. [Online]. Available: http://www.fda.gov/OHRMS/DOCKETS/98fr/04-10447.pdf [accessed July 8, 2005].

FDA. 2004f. *Enforcement Report—April 7, 2004*. [Online]. Available: http://www.fda.gov/bbs/topics/enforce/2004/ENF00842.html [accessed July 8, 2005].

FDA. 2004g. *Enforcement Report—January 21, 2004*. [Online]. Available: http://www. fda.gov/bbs/topics/enforce/2004/ENF00831.html [accessed July 8, 2005].

FDA. 2004h. *Enforcement Report—July 21, 2004*. [Online]. Available: http://www.fda.gov/bbs/topics/enforce/2004/ENF00857.html [accessed July 8, 2005].

FDA. 2004i. *Enforcement Report—November 3, 2004*. [Online]. Available: http://www.fda.gov/bbs/topics/enforce/2004/ENF00872.html [accessed July 8, 2005].

FDA. 2004j. FDA recall policies. In: *Center for Food Safety and Applied Nutrition Industry Affairs Staff Brochure*. Rockville, MD: FDA. [Online]. Available: http://vm.cfsan.fda.gov/~lrd/recall2.html [accessed July 8, 2005].

FDA. 2004k. *FDA Statement on Recommendations of the Psychopharmacologic Drugs and Pediatric Advisory Committees*. [Online]. Available: http://www.fda.gov/bbs/topics/news/2004/NEW01116.html [accessed July 8, 2005].

FDA. 2004l. *FDA Talk Paper: FDA Issues Public Health Advisory on Cautions for Use of Antidepressants in Adults and Children*. [Online]. Available: http://www.fda.gov/bbs/topics/ANSWERS/2004/ANS01283.html [accessed July 8, 2005].

FDA. 2004m. *Frequently Asked Questions*. [Online]. Available: http://www.fda.gov/cber/faq.htm [accessed July 8, 2005].

FDA. 2004n. *FY 2004 ODE/OIVD Annual Report*. [Online]. Available: http://www.fda.gov/cdrh/annual/fy2003/ode/part3.html [accessed July 8, 2005].

FDA. 2004o. Global Harmonization Task Force, study groups 1, 2, 3, and 4; New proposed and final documents; Availability. *Federal Register* 69(32):7650–7652. [Online]. Available: http://a257.g.akamaitech.net/7/257/2422/14mar20010800/edocket.access.gpo.gov/2004/pdf/04-3412.pdf [accessed July 8, 2005].

FDA. 2004p. *Guidance for Industry and FDA Staff: Premarket Assessment of Pediatric Medical Devices*. Rockville, MD: FDA. [Online]. Available: http://www.fda.gov/cdrh/mdufma/guidance/1220.pdf [accessed July 8, 2005].

FDA. 2004q. *Instructions for Completing the MedWatch Form 3500A*. [Online]. Available: http://www.fda.gov/medwatch/report/instruc.htm#obtain_and_send [accessed July 8, 2005].

FDA. 2004r. *Medical Device Exemptions 510(k) and GMP Requirements*. [Online]. Available: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpcd/315.cfm [accessed July 8, 2005].

FDA. 2004s. *Medical Device Recalls—Class 1 Recall: Biliary Stents Instructions for Use*. [Online]. Available: http://www.fda.gov/cdrh/recalls/recall-050404.html [accessed July 8, 2005].

FDA. 2004t. *Medical Devices and Radiological Health Fiscal Year 2005*. [Online]. Available: http://www.fda.gov/oc/oms/ofm/budget/2005/devices.htm [accessed July 8, 2005].

FDA. 2004u. *Nellcor Announces Nationwide Voluntary Recall of All CapnoProbe™ Sublingual Sensors*. [Online]. Available: http://www.fda.gov/oc/po/firmrecalls/nellcor08_04.html [accessed July 8, 2005].

FDA. 2004v. Postmarket surveillance: Medical device adverse event reporting. *FY 2003 CDRH Annual Report: Assuring Safe Products in the Market*. Rockville, MD: FDA. [Online]. Available: http://www.fda.gov/cdrh/annual/fy2003/assuring.html [accessed July 8, 2005].

FDA. 2004w. *Premarket Notification [510(k)]*. [Online]. Available: http://www.fda.gov/cdrh/devadvice/314.html [accessed July 8, 2005].

FDA. 2004x. Report on the performance of drug and biologics firms in conducting postmarketing commitment studies; Availability. *Federal Register* 69(50):12162–12164. [Online]. Available: http://www.fda.gov/OHRMS/DOCKETS/98fr/04-5757.htm [accessed July 8, 2005].

FDA. 2004y. *Report to Congress: Barriers to the Availability of Medical Devices Intended for the Treatment or Diagnosis of Diseases and Conditions That Affect Children*. Washington, DC: FDA. [Online]. Available: http://www.fda.gov/cdrh/pediatricdevices/rtc100104.html [accessed July 8, 2005].

FDA. 2004z. *Voluntary Reporting by Health Professionals*. [Online]. Available: http://www.fda.gov/medwatch/report/hcp.htm [accessed July 8, 2005].

FDA. 2005a. *CDRH Organization Structure*. [Online]. Available: http://www.fda.gov/cdrh/organiz.html [accessed July 8, 2005].

FDA. 2005b. *FDA Enforcement Report Index*. [Online]. Available: http://www.fda.gov/opacom/Enforce.html [accessed July 8, 2005].

FDA. 2005c. Headgear safety: Getting it straight. *FDA & You* 6(Spring):1–3. [Online]. Available: http://www.fda.gov/cdrh/fdaandyou/issue06.pdf [accessed July 8, 2005].

FDA. 2005d. *Medical Product Safety Information*. [Online]. Available: http://www.fda.gov/medwatch/safety.htm [accessed July 8, 2005].

FDA. 2005e. *Product Classification Database—Dental Mercury*. [Online]. Available: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpcd/classification.cfm?id=896 [accessed July 8, 2005].

FDA. 2005f. *Product Classification Database—Mechanical Wheelchair*. [Online]. Available: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPCD/classification.cfm?ID=2488 [accessed July 8, 2005].

FDA. 2005g. *Product Classification Database—Surgeon Gloves*. [Online]. Available: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPCD/classification.cfm?ID=3231 [accessed July 8, 2005].

FDA. 2005h. *Public Health Notifications*. [Online]. Available: http://www.fda.gov/cdrh/safety.html [accessed July 8, 2005].

FDA. 2005i (February 15). Reforms will improve oversight and openness at FDA. *Department of Health and Human Services News Release* [Online]. Available: http://www.hhs.gov/news/press/2005pres/20050215.html [accessed July 8, 2005].

FDA. 2005j. Report on the performance of drug and biologics firms in conducting postmarketing commitment studies; availability. *Federal Register* 70(33):8379–8381. [Online]. Available: http://www.fda.gov/OHRMS/DOCKETS/98fr/05-3221.htm [accessed July 8, 2005].

FDA. No date. *Timeline: Chronology of Drug Evaluation and Research in the United States*. [Online]. Available: http://www.fda.gov/cder/about/history/time1.htm [accessed July 8, 2005].

Feigal D (for Center for Devices and Radiological Health). 2001a (April 27). Letter to Colleague re: FDA Public Health Notification: Problems with Endovascular Grafts for Treatment of Abdominal Aortic Aneurysm (AAA). [Online]. Available: http://www.fda.gov/cdrh/safety/aaa.pdf [accessed July 8, 2005].

Feigal D (for Center for Devices and Radiological Health). 2001b (November 2). Letter to Radiologists, Radiation Health Professionals Risk Managers and Hospital Administrators re: FDA Public Health Notification: Reducing Radiation Risk from Computed Tomography for Pediatric and Small Adult Populations. [Online]. Available: http://www.fda.gov/cdrh/safety/110201-ct.pdf [accessed July 8, 2005].

Feigal D. 2002. *CDRH Vision—Total Product Lifecycle*. (Unpublished). Available: http://www.fda.gov/ohrms/dockets/ac/01/slides/3799s1_11_Feigal/ [accessed July 8, 2005].

Feigal D (for Center for Devices and Radiological Health). 2003 (December 17). Letter to Colleague re: FDA Public Health Notification: Updated on Mortality Associated with Medtronic AVE AneuRx® Stent Graft System. [Online]. Available: http://www.fda.gov/cdrh/safety/aneurx.html [accessed July 8, 2005].

Felker GM, Thompson RE, Hare JM, Hruban RH, Clemetson DE, Howard DL, Baughman KL, Kasper EK. 2000. Underlying causes and long-term survival in patients with initially unexplained cardiomyopathy. *New England Journal of Medicine* 342(15):1077–1122.

Ferguson G, Eliasziw M, Barr H, Clagett G, Barnes R, Wallace M, Taylor D, Haynes R, Finan J, Hachinski V, Barnett H. 1999. The North American Symptomatic Carotid Endarterectomy Trial: Surgical results in 1415 patients. *Stroke* 30(9):1751–1758.

Flannery, E. 2002. *Food and Drug Administration Requirements Applicable to the Marketing of a Medical Device*. (Unpublished).

Fletcher DM. 2004. Achieving data quality: New data from a pediatric health information system earns the trust of its users. *Journal of American Health Information Management Association* 75(10):22–26.

Flynn JM, Luedtke LM, Ganley TJ, Dawson J, Davidson RS, Dormans JP, Ecker ML, Gregg JR, Horn BD, Drummond DS. 2004. Comparison of titanium elastic nails with traction and a spica cast to treat femoral fractures in children. *Journal of Bone and Joint Surgery* 86(4):770–777.

Fratino G, Mazzola C, Buffa P, Torre M, Castagnola E, Magillo P, Molinari A. 2001. Mechanical complications related to indwelling central venous catheter in pediatric hematology/oncology patients. *Pediatric Hematology and Oncology* 18(5):317–324.

Freeman T, Vawter D, Leaverton P, Godbold J, Hauser R, Goetz C, Olanow C. 1999. Use of placebo surgery in controlled trials of a cellular-based therapy for Parkinson's disease. *New England Journal of Medicine* 341(13):988–992.

Friedman L, Furberg C, DeMets D. 1985. *Fundamentals of Clinical Trials*. 2nd ed. St. Louis, MO: Mosby Year Book.

Friis R, Sellers T. 2004. *Epidemiology for Public Health Practice*. 3rd ed. Sudbury, MA: Jones and Bartlett.

Frush DP. 2003. MDCT: Risk and reward. *Decisions in Imaging Economics*. Unpaged. [Online]. Available: http://www.imagingeconomics.com/library/200310-09.asp [accessed July 8, 2005].

Frush DP, Donnelly LF. 2001 (December). Reduced radiation dose limits risk of pediatric CT. *Diagnostic Imaging Supplement*. Unpaged. [Online]. Available: http://www.diagnosticimaging.com/advancedCT/reduced-frush.jhtml?_requestid=929172 [accessed July 8, 2005].

GAO (General Accounting Office [now the Government Accountability Office]). 1986. *Medical Devices: Early Warning of Problems Is Hampered by Severe Underreporting*. Washington, DC: GAO.

GAO. 1989. *Medical Devices: FDA's Implementation of the Medical Device Reporting Regulation*. Washington, DC: GAO.

GAO. 1997. *Medical Device Reporting: Improvement Needed in FDA's System for Monitoring Problems for Approved Devices*. Washington, DC: GAO. [Online]. Available: http://www.fda.gov/cdrh/hes9721.pdf [accessed July 8, 2005].

GAO. 2004. *Data to Measure the Timeliness of Reviews of Medical Device Applications Are Limited*. [Online]. Available: http://www.fda.gov/cdrh/mdufma/reports/gao-04-1022.pdf [accessed July 8, 2005].

Gardner S, Flack M. 1999. *Designing a Medical Device Surveillance Network: Report to Congress*. Rockville, MD: FDA. [Online]. Available: http://www.fda.gov/cdrh/postsurv/medsun.html [accessed July 8, 2005].

Geha A, Laks H, Stansel Jr H, Cornhill J, Kilman J, Buckley M, Roberts W. 1979. Late failure of porcine valve heterografts in children. *Journal of Thoracic and Cardiovascular Surgery* 78(3):351–364.

GHTF (Global Harmonization Task Force). 2002. *Medical Devices: Post Market Surveillance: National Competent Authority Report Exchange Criteria*. Brussels, Belgium: GHTF. [Online]. Available: http://www.ghtf.org/sg2/inventorysg2/sg2-n20r10.pdf [accessed July 8, 2005].

Giedd J. 2004. Structural magnetic resonance imaging of the adolescent brain. *Annals of the New York Academy of Sciences* 1021:77–85.

Gilmore H. 1990. Medical treatment of hydrocephalus. In: Scott R, ed. *Concepts in Neurosurgery: Hydrocephalus*. Vol. 3. Baltimore, MD: Williams and Wilkins. Pp. 37–46.

Giroud D. 2004. A revised guideline for medical device clinical investigations: ISO 14155 part 1 and 2:2003. *The Quality Assurance Journal* 8:1–4. [Online]. Available: http://www.d-target.com/04nouvelles%20pages/articles/article_04.pdf [accessed July 8, 2005].

Glass P, Bulas D, Wagner A, Rajasingham S, Civitello L, Papero P, Coffman C, Short B. 1997. Severity of brain injury following neonatal extracorporeal membrane oxygenation and outcome at age 5 years. *Developmental Medicine and Child Neurology* 39(7):441–448.

Gooch J, Oberg W, Grams B, Ward L, Walker M. 2003. Complications of intrathecal baclofen pumps in children. *Pediatric Neurosurgery* 39:1–6.

Good W. 2001. Cataract surgery in young children. *British Journal of Ophthalmology* 85(3): 254.

Grassley C. 2004 (March 25). Letter to Secretary Tommy G. Thompson re: Grassley Questions FDA's Handling of Research on Antidepressants, Suicide. [Online]. Available: http://www.senate.gov/~finance/press/Gpress/2004/prg032504b.pdf [accessed July 8, 2005].

Graziani L, Gringlas M, Baumgart S. 1997. Cerebrovascular complications and neurodevelopmental sequelae of neonatal ECMO. *Clinics in Perinatology* 24(3):655–675.

Greene P. 2005. Deep-Brain Stimulation for Generalized Dystonia. *New England Journal of Medicine* 352(5):498–500.

Greenfield L. 2004. Regarding "Withdrawal of article by the FDA after objection from Medtronic." *Journal of Vascular Surgery* 40(3):594.

Gregory G, Kitterman J, Phibbs R, Tooley W, Hamilton W. 1971. Treatment of the idiopathic respiratory-distress syndrome with continuous positive airway pressure. *New England Journal of Medicine* 284(24):1333–1340.

Groopman J. 2005 (January 10). The pediatric gap: Why have most medications never been properly tested on kids? *The New Yorker*. Pp. 32–37.

Gross TP. 1996. *Human Factors and Postmarket Surveillance at FDA*. Rockville, MD: FDA. [Online]. Available: http://www.fda.gov/cdrh/humfac/hufactpg.html [accessed July 8, 2005].

Gross TP. 2004 (April 15). Presentation to the Committee on Postmarket Surveillance of Pediatric Medical Devices, Washington, DC. Institute of Medicine.

H010002 (Food and Drug Administration). 2001. Stryker Biotech. *Approved Labeling: OP-1™ Implant*. [Online]. Available: http://www.fda.gov/cdrh/pdf/h010002d.pdf [accessed July 8, 2005].

H020003 (Food and Drug Administration). 2003 (November 21). Letter to Donna Saito, Medtronic Inc. re: PMA Approval of Contegra® Valved Conduit, Models 200 (unsupported) and 200S (supported). [Online]. Available: http://www.fda.gov/cdrh/pdf2/H020003a.pdf [accessed July 8, 2005].

H020007 (Food and Drug Administration). 2003. *Summary of Safety and Probable Benefit: Medtronic Activa® Dystoinia Therapy*. [Online]. Available: http://www.fda.gov/cdrh/pdf2/H020007b.pdf [accessed July 8, 2005].

H030003 (Food and Drug Administration). 2004a (February 25). Letter to Timothy R. Placek, MicroMed Technology Inc. re: PMA Approval of DeBakey VAD® Child Left Ventricular Assist System. [Online]. Available: http://www.fda.gov/cdrh/pdf3/H030003a.pdf [accessed July 8, 2005].

H030003 (Food and Drug Administration). 2004b. *Summary of Safety and Probable Benefit: DeBakey VAD® Child System for Humanitarian Use in Pediatric Patients*. [Online]. Available: http://www.fda.gov/cdrh/pdf3/H030003b.pdf [accessed July 8, 2005].

H030009 (Food and Drug Administration). 2004a (August 24). Letter to John Walsh, Synthes re: PMA Approval of Synthes Spine Vertical Expendable Prosthetic Titanium Rib. [Online]. Available: http://www.fda.gov/cdrh/PDF3/h030009a.pdf [accessed July 8, 2005].

H030009 (Food and Drug Administration). 2004b. *Summary of Safety and Probable Benefit: Synthes Spine Vertical Expendable Prosthetic Titanium Rib*. [Online]. Available: http://www.fda.gov/cdrh/PDF3/h030009b.pdf [accessed July 8, 2005].

H030009 (Food and Drug Administration). 2004c. *Draft Package Inset: Synthes Spine Vertical Expendable Prosthetic Titanium Rib*. [Online]. Available: http://www.fda.gov/cdrh/PDF3/h030009c.pdf [accessed July 8, 2005].

Halperin W, Baker E, Monson R. 1992. *Public Health Surveillance*. New York, NY: Van Nostrand Reinhold.

Harder B. 2004 (August 31). Comments before the Committee on Postmarket Surveillance of Pediatric Medical Devices, Washington, DC, Institute of Medicine.

Harder N. 2004 (August 31). Comments before the Committee on Postmarket Surveillance of Pediatric Medical Devices, Washington, DC, Institute of Medicine.

Harmon W, Sleeper L, Cuniberti L, Messere J, Colan S, Orav E, Towbin J, Lipshultz S. 2004 (May 4). *Dilated cardiomyopathy: An analysis of therapy offered to children enrolled in the Pediatric Cardiomyopathy Registry*. Platform Presentation at the Pediatric Academic Societies Annual Meeting, San Francisco, CA.

Harris G. 2004 (November 19). FDA failing in drug safety, official asserts. *New York Times*. P. A1.

Haskal Z, Leen V, Thomas-Hawkins C, Shlansky-Goldberg R, Baum R, Soulen M. 1996. Transvenous removal of fibrin sheaths from tunneled hemodialysis catheters. *Journal of Vascular and Interventional Radiology* 7(4):513–517.

Hazinski M, Zaritsky A, Nadkarni V, Hickey R, Schexnayder S, Berg R, eds. 2002. *PALS Provider Manual*. Dallas, TX: American Heart Association.

Heeney v. FDA (*John Heeney, Plaintiff-Appellant v. Food and Drug Administration, Defendant-Appellee, Boston Scientific Corporation, Defendant-Intervenor-Appellee*). 2001. 7 Fed. Appx. 770 (9th Cir. Cal).

Hefflin BJ, Gross TP, Schroeder TJ. 2004. Estimates of medical device-associated adverse events from emergency departments. *American Journal of Preventive Medicine* 27(3):246–253.

Hermida J, Nicholas D, Blumenfeld S. 1999. Methodology matters. Comparative validity of three methods for assessment of the quality of primary health care. *International Journal for Quality in Health Care* 11(5):429–433.

Hevesi AG. 2003. *Maintaining Information on Adverse Patient Incidents at Hospitals and Clinics*. Albany, NY: New York State Office of the State Comptroller. [Online]. Available: http://www.osc.state.ny.us/audits/allaudits/093004/03s27.pdf [accessed July 8, 2005].

Higgs R. 1995. Wrecking ball: FDA regulation of medical devices. *Cato Policy Analysis* 235 [Online]. Available: http://www.cato.org/pubs/pas/pa-235es.html [accessed July 8, 2005].

Hilzenrath DS. 2003 (June 13). Firm silent as patients died: Device maker pleads guilty to misleading FDA. *Washington Post*. P. A1. [Online]. Available: http://www. washingtonpost.com/ac2/wp-dyn?pagename=article&contentId=A51530-2003Jun12&notFound=true [accessed July 8, 2005].

Hoffman J, Kaplan S, Liberthson R. 2004. Prevalence of congenital heart disease. *American Heart Journal* 147(3):425–439.

Horton R. 2004. Vioxx, the implosion of Merck, and aftershocks at the FDA. *Lancet* 364 (9450):1995–1996.

Huch A, Seiler D, Meinzer K, Huch R, Galster H, Lubbers D. 1977. Transcutaneous PCO2 measurement with a miniaturised electrode. *Lancet* 1(8019):982–983.

Hutt P. 1989. A history of government regulation of adulteration and misbranding of medical devices. *Food Drug Cosmetic Law Journal* 44:99–117.

Hutt P, Merrill R. 1991. *Food and Drug Law: Cases and Materials*. Westbury, NY: The Foundation Press.

ICH (International Conference on Hamonisation). 1996. *Guideline for Good Clinical Practice: E6*. Geneva, Switzerland: ICH. [Online]. Available: http://www.ich.org/MediaServer.jser?@_ID=487&@_TYPE=MULTIMEDIA&@_TEMPLATE=616&@_MODE=GLB [accessed July 8, 2005].

ICH. 2000. *Clinical Investigation of Medicinal Products in the Pediatric Population: E11*. Geneva, Switzerland: ICH. [Online]. Available: http://www.ich.org/MediaServer.jser?@_ID=487&@_TYPE=MULTIMEDIA&@_TEMPLATE=616&@_MODE=GLB [accessed July 8, 2005].

IOM (Institute of Medicine). 1990. *Medicare: A Strategy for Quality Assurance, Volume II: Sources and Methods*. Washington, DC: Institute of Medicine.

IOM. 1992. *Guidelines for Clinical Practice: Development to Use*. Washington, DC: National Academy Press.

IOM. 2000a. *Extending Medicare Reimbursement to Clinical Trials*. Washington, DC: National Academy Press.

IOM. 2000b. *Rational Therapeutics for Infants and Children: Workshop Summary*. Washington, DC: National Academy Press.

IOM. 2000c. *To Err Is Human: Building a Safer Health System*. Washington, DC: National Academy Press.

IOM. 2003. *Responsible Research: A Systems Approach to Protecting Research Participants*. Washington, DC: The National Academies Press.

IOM. 2004a. *Ethical Conduct of Clinical Research Involving Children*. Washington, DC: The National Academies Press.

IOM. 2004b. *Patient Safety: Achieving a New Standard for Care*. Washington, DC: The National Academies Press.

ISMP (Institute for Safe Medication Practices). 2001. Hazard alert! Asphyxiation possible with syringe tip caps. Do not provide hypodermic syringes to parents for administering oral liquids to children. *Medication Safety Alert*. Unpaged. [Online]. Available: http://www.ismp.org/MSAarticles/Hypodermic.html [accessed July 8, 2005].

ISMP. 2003. Blood pressure monitor tubing may connect to IV ports. *Medication Safety Alert* [Online]. Available: http://www.ismp.org/MSAarticles/blood.htm [accessed July 8, 2005].

ISO (International Organization for Standardization). 2000. *ISO 9001: Quality Management Systems: Requirements*. Geneva, Switzerland: ISO. [Online]. Available: http://www.iso.org/iso/en/CatalogueDetailPage.CatalogueDetail?CSNUMBER=21823&ICS1=3&ICS2=120&ICS3=10 [accessed July 8, 2005].

ISO. 2003a. Part 1: General requirements. In: *ISO 14155: Clinical Investigation of Medical Devices for Human Subjects*. Geneva, Switzerland: ISO.

ISO. 2003b. Part 2: Clinical investigation plans. In: *ISO 14155: Clinical Investigation of Medical Devices for Human Subjects*. Geneva, Switzerland: ISO.

ISO. 2004. *About ISO*. [Online]. Available: http://www.iso.org/iso/en/aboutiso/introduction/index.html [accessed July 8, 2005].

Jacobs P. 2003 (August 3). Medical firm's dangerous secret. *San Jose Mercury News*. Unpaged. [Online]. Available: http://www.yourlawyer.com/practice/news.htm?story_id= 6390&topic=Medical%20Malpractice [accessed July 8, 2005].

Janssen WF. 1981a. The story of the laws behind the labels: Part I. 1906 Food and Drugs Act. *FDA Consumer* [Online]. Available: http://vm.cfsan.fda.gov/~lrd/history1.html [accessed July 8, 2005].

Janssen WF. 1981b. The story of the laws behind the labels: Part II. 1938 The Federal Food, Drug, and Cosmetic Act. *FDA Consumer* [Online]. Available: http://vm.cfsan.fda.gov/~lrd/histor1a.html [accessed July 8, 2005].

Janssen WF. 1981c. The story of the laws behind the labels: Part III. 1962 Drug Amendments. *FDA Consumer* [Online]. Available: http://vm.cfsan.fda.gov/~lrd/histor1b.html [accessed July 8, 2005].

JCAHO (Joint Commission on Accreditation for Healthcare Organizations). 2003. Preventing surgical fires. *Sentinel Event Alert* 29:1. [Online]. Available: http://www.jcaho.org/about+us/news+letters/sentinel+event+alert/sea_29.htm [accessed July 8, 2005].

JCAHO. 2004. *Sentinel Event Statistics: Root Causes of Perinatal Deaths and Injuries (1995–2004)*. [Online]. Available: http://www.jcaho.org/accredited+organizations/ambulatory+care/sentinel+events/root+causes+of+sentinel+event.htm.

JCAHO. 2005a. *Sentinel Event Policy and Procedures—Updated June 2005*. [Online]. Available: http://www.jcaho.org/accredited+organizations/sentinel+event/se_pp.htm#1 [accessed July 8, 2005].

JCAHO. 2005b. *Sentinel Event Statistics—December 31, 2004*. [Online]. Available: http://www.jcaho.org/accredited+organizations/ambulatory+care/sentinel+events/sentinel+event+statistics.htm [accessed March 3, 2005].

Jennis M, Peabody J. 1987. Pulse oximetry: An alternative method for the assessment of oxygenation in newborn infants. *Pediatrics* 79(4):524–528.

Johnson C. 2003. The interaction between safety culture and uncertainty over device behaviour: The limitations and hazards of telemedicine. In: *International Systems Safety Conference*. Glasgow, Scotland: University of Glasgow. Pp. 273–283. [Online]. Available: http://www.dcs.gla.ac.uk/~johnson/papers/ISSC2003/telemedicine.pdf [accessed July 8, 2005].

Johnson C. Submitted for publication. *Why Did That Happen? A Brief Explanation for the Proliferation of Barely Usable Software in Healthcare Applications*. [Online]. Available: http://www.dcs.gla.ac.uk/~johnson/papers/Chris_Johnson_Usability.pdf [accessed July 8, 2005].

Johnson FE, Virgo KS, eds. In Press. Databases for studying the epidemiology of implanted medical devices. In: *The Bionic Human: Health Promotion for People with Implanted Prosthetic Devices*. Humana Press: Totowa, New Jersey.

Johnston M, Nishimura A, Harum K, Pekar J, Blue M. 2001. Sculpting the developing brain. *Advances in Pediatrics* 48:1–38.

Jurasek G. 2003. Lessons from the bronchoscope recall. *Pulmonary Reviews.com: Trends in Pulmonary and Critical Care Medicine* 8(3): Unpaged. [Online]. Available: http://www.pulmonaryreviews.com/mar03/pr_mar03_brochoscope.html [accessed July 8, 2005].

K003819 (Food and Drug Administration). 2001 (May 2). Letter to Teresa Skarr, Agilent Technologies, re: Review of 510(k) Notification and Determination of Substantial Equivalence for Heartstream FR2 AEDs with Attenuated Defibrillation Pads. [Online]. Available: http://www.fda.gov/cdrh/pdf/k003819.pdf [accessed July 8, 2005].

K014241 (Food and Drug Administration). 2003 (August 1). Letter to Kenneth A. Collins, Alsius Corporation re: Review of 510(k) Notification and Determination of Substantial Equivalence for Alsius CoolGard and Cool Line Catheter Thermal Regulation System. [Online]. Available: http://www.fda.gov/cdrh/pdf/k014241.pdf [accessed July 8, 2005].

K021489 (Food and Drug Administration). 2002 (December 4). Letter to Ehab M. Esmail, Wright Medical Technology Inc. re: Review of 510(k) Notification and Determination of Substantial Equivalence for REPIPHYSIS Limb Salvage System. [Online]. Available: http://www.fda.gov/cdrh/pdf2/k021489.pdf [accessed July 8, 2005].

Kahan JS. 1996 (May). Twenty years of FDA device regulation: FDA regulatory programs: Cooperation and common sense typify a record of success. *Medical Device and Diagnostic Industry*. Pp. 88–89. [Online]. Available: http://www.devicelink.com/mddi/archive/96/05/011.html [accessed July 8, 2005].

Karuga C. 2003. *The Expansion of FDA's Enforcement Powers from 1906–2003 (2003 Third Year Paper)*. Cambridge, MA: Harvard. [Online]. Available: http://leda.law.harvard.edu/leda/data/616/Karuga.pdf [accessed July 8, 2005].

Katcher M, Shapiro M, Guist C. 1986. Severe injury and death associated with home infant cardiorespiratory monitors. *Pediatrics* 78(5):775–779.

Kaye RD, North RA, Peterson MK. 2003. *UPCARE: An Analysis, Description, and Educational Tool for Medical Devices Use Problems*. Proceedings of the Eighth Annual International Conference of Industrial Engineering Theory Applications and Practice, Las Vegas, NV.

Kearns G, Winter H. 2003. Proton pump inhibitors in pediatrics: Relevant pharmacokinetic and pharmacodynamics. *Journal of Pediatric Gastroenterology and Nutrition* 37 (Supp 1): S52–S59.

Kelley A, Schochet T, Landry C. 2004. Risk taking and novelty seeking in adolescence: Introduction to part I. *Annals of the New York Academy of Sciences* 1021:27–32.

Kirschke D, Jones T, Craig A, Chu P, Mayernick G, Patel J, Schaffner W. 2003. Pseudomonas aeruginosa and Serratia marcescens contamination associated with a manufacturing defect in bronchoscopes. *New England Journal of Medicine* 348(3):214–220.

Knelson M, Hudson E, Suhochi P, Payne C, Sallee D, Newman G. 1995. Functional restoration of occluded central venous catheters: New interventional techniques. *Journal of Vascular and Interventional Radiology* 6(4):623–627.

Kong P. 2004 (July 19). Letter to FDA (Food and Drug Administration) re: 2004N-0254 - Possible Barriers to the Availability of Medical Devices Intended to Treat or Diagnose Diseases and Conditions that Affect Children; Request for Comments. [Online]. Available: http://www.fda.gov/ohrms/dockets/dailys/04/july04/071904/04N-0254-ec1.htm [accessed July 8, 2005].

Kozak L, Owings M, Hall M. 2004. National Hospital Discharge Summary: 2001 annual summary with detailed diagnosis and procedure data. *Vital and Health Statistics* 13(156):2. [Online]. Available: http://www.cdc.gov/nchs/data/series/sr_13/sr13_156.pdf [accessed July 8, 2005].

Kurtzweil P. 1994. Avoiding problems: Liquid medication and dosing devices. *FDA Consumer Magazine* 28(8): Unpaged. [Online]. Available: http://www.fda.gov/fdac/reprints/drugdose.html [accessed July 8, 2005].

Langmoen I, Lundar T, Vatne K, Hovind K. 1992. Occurrence and management of fractured peripheral catheters in CSF shunts. *Child's Nervous System* 8(4):222–225.

Lantos J, Kohrman A. 1992. Ethical aspects of pediatric home care. *Pediatrics* 89(5 Pt 1):920–924.

Laskey AL, Dyer C, Tobias JD. 2002. Venous air embolism during home infusion therapy. *Pediatrics* 109(1):E15.

Le B, Eyre J, Wehby M, Wheatley M. 2001. Intracranial migration of halo fixation pins: A complication of using an extraoral distraction device. *Cleft Palate-Craniofacial Journal* 38(4):401–404.

Liebman J, Cullum L, Belloc N. 1969. Natural history of transposition of the great arteries. Anatomy and birth and death characteristics. *Circulation* 40(2):237–262.

Liem M, van der Graaf Y, van Vroonhoven T. 1997. CONSORT, randomized trials and the surgical scientific community. *British Journal of Surgery* 84(6):769–770.

Luciana M. 2003. Cognitive development in children born preterm: Implications for theories of brain plasticity following early injury. *Development & Psychopathology* 15(4):1017–1047.

Lumpkin JR. 2004 (January 29). Letter to The Honorable Tommy G. Thompson re: Consolidated Health Informations Initiative (CHI) Recommendations for Specific Patient Medical Record Information (PMRI) Terminology Standards. [Online]. Available: http://www.ncvhs.hhs.gov/040129lt.pdf [accessed July 8, 2005].

Mast J. 2004. Statement for the Committee on Postmarket Surveillance of Pediatric Medical Devices. Washington, DC. Institute of Medicine.

Mathews AW, Burton TM. 2004 (July 9). Invasive procedure after Medtronic lobbying push, the FDA had change of heart: Agency squelches an article raising doubts on safety of device to repair artery threat of 'criminal sanction.' *The Wall Street Journal*. P. A1.

McCormick M, Kass B, Elixhauser A, Thompson J, Simpson L. 2000. Annual report on access to and utilization of health care for children and youth in the United States—1999. *Pediatrics* 105(1 Pt 3):219–230.

McGirt M, Zaas A, Fuchs H, George T, Kaye K, Sexton D. 2003. Risk factors for pediatric ventriculoperitoneal shunt infection and predictors of infectious pathogens. *Clinical Infectious Diseases* 36(7):858–862.

McKneally M, Daar A. 2003. Introducing new technologies: Protecting subjects of surgical innovation and research. *World Journal of Surgery* 27(8):930–934.

MedSun. 2004 (May). Special surveys of MedSun sites. *MedSun News*. P. 2.

Medtronic. 2005. *News Release: Medtronic Issues Notification Regarding Certain Implantable Defibrillator Models*. Minneapolis, MN: Medtronic. [Online]. Available: http://www.fda.gov/cdrh/cdrhhhc/brochure-checklist.html [accessed July 8, 2005].

Meier B. 2005 (April 1). FDA report criticizes oversight of medical device makers. *New York Times*. P. C3.

Meinert C. 1998. Beyond CONSORT: Need for improved reporting standards for clinical trials. *Journal of the American Medical Association* 279:1487–1489.

Merrill R. 1994. Regulation of drugs and devices: An evolution. *Health Affairs* 13(3):47–69. [Online]. Available: http://content.healthaffairs.org/cgi/reprint/13/3/47.pdf [accessed July 8, 2005].

Moher D. 1998. CONSORT: An evolving tool to help improve the quality of reports of randomized controlled trials. *Journal of the American Medical Association* 279:1489–1491.

Moher D, Schulz K, Altman D, for the CONSORT Group. 2001. The CONSORT statement: Revised recommendations for improving the quality of reports of parallel-group randomized trials. *Journal of the American Medical Association* 285(15):1987–1991.

Mohr J, Batalden P. 2002. Improving safety on the front lines: The role of clinical microsystems. *Quality and Safety in Health Care* 11(1):45–50.

Mol A, Bouten C, Baaijens F, Zund G, Turina M, Hoerstrup S. 2004. Review article: Tissue engineering of semilunar heart valves: Current status and future developments. *Journal of Heart Valve Disease (England)* 13(2):272–280.

Moodie AM. 2000. S*ummary Minutes of the Gastroenterology and Urology Device Advisory Panel Meeting—Open Session, Food and Drug Administration*. [Online]. Available: http://www.fda.gov/ohrms/dockets/ac/00/minutes/3653m1.pdf [accessed July 8, 2005].

Moss R, Henry M, Dimmitt R, Rangel S, Geraghty N, Skarsgard E. 2001. The role of prospective randomized clinical trials in pediatric surgery: State of the art? *Journal of Pediatric Surgery* 36(8):1182–1186.

Munsey RR. 1995. Trends and events in FDA regulation of medical devices over the last fifty years. *Food and Drug Law Journal* 50(Special Issue):163–177.

Murff HJ, Gosbee JW, Bates DW. 2001. Human factors and medical devices. In: Markowitz AJ, ed. *Making Health Care Safer: A Critical Analysis of Patient Safety Practices Evidence Report/Technology Assessment*. Vol. 43. Rockville, MD: AHRQ. [Online]. Available: http://www.ahrq.gov/clinic/ptsafety/chap41a.htm [accessed July 8, 2005].

NACHRI (National Association of Children's Hospitals and Related Institutions). 2003. *History of Children's Hospitals*. [Online]. Available: http://www.childrenshospitals.net/template.cfm?section=home&contentid=7418&template=/contentmanagement/contentdisplay.cfm [accessed July 8, 2005].

Nature Publishing Group. 2005. Editorial: Drug safety on trial. *Nature* 434(7033):545.

NCI (National Cancer Institute) and SPR (Society for Pediatric Radiology). 2002. *Radiation & Pediatric Computed Tomography: A Guide for Health Care Providers*. Rockville, MD: NCI. [Online]. Available: http://www.cancer.gov/PDF/15c2faba-f327-43c0-8503-dcd64c272e59/CTNewsletter.pdf [accessed July 8, 2005].

NCIPC (National Center for Injury Prevention and Control). 2001. *WISQARS Injury Mortality Reports, 1999–2001*. Atlanta, GA: CDC. [Online]. Available: http://webappa.cdc.gov/sasweb/ncipc/mortrate10_fy.html [accessed July 8, 2005].

NCIPC. 2002. *WISQARS Nonfatal Injury Reports*. Atlanta, GA: CDC. [Online]. Available: http://webappa.cdc.gov/sasweb/ncipc/nfirates2001.html [accessed July 8, 2005].

NERI (New England Research Institutes). 2004. *Pediatric Cardiomyopathy Registry (PCMR)*. [Online]. Available: http://www.neri.org/html/research/clinical/pediatric.asp [accessed July 8, 2005].

Neuenschwander S, Hoerstrup S. 2004. Heart valve tissue engineering. *Transplant Immunology* 12(3-4):359–365.

New York State Department of Health. 2004. *State Health Commissioner Novello, Comptroller Announce Changes in System Tracking Accidental Deaths, Injuries in Hospitals & Clinics*. [Online]. Available: http://www.health.state.ny.us/press/releases/2004/nyports_tracking_accidental_deaths_9-28-2004.htm [accessed July 8, 2005].

NHRPAC (National Human Research Protections Advisory Committee). 2001. *Children's Workgroup Report (Draft)*. [Online]. Available: http://www.hhs.gov/ohrp/nhrpac/mtg04-01/child-workgroup4-5-01.pdf [accessed July 8, 2005].

Niehaus M, Tebbenjohanns J. 2001. Editorial: Electromagnetic interference in patients with implanted pacemakers or cardioverter-defibrillators. *Heart* 86(3):246–248.

NIH (National Institutes of Health). 1998. *NIH Policy and Guidelines on the Inclusion of Children As Participants in Research Involving Human Subjects, March 6, 1998*. Bethesda, MD: NIH. [Online]. Available: http://grants1.nih.gov/grants/guide/notice-files/not98-024.html [accessed July 8, 2005].

NIH. 2000. Improving medical implant performance through retrieval information: Challenges and opportunities. In: *State of the Science Statements: National Institutes of Health's 2000 NIH Technology Assessment Conference Summary*. [Online]. Available: http://consensus.nih.gov/ta/019/019_statement.htm [accessed July 8, 2005].

Niparko JK. 2004 (June 24). Panel Discussion before the Committe on Postmarket Surveillance of Pediatric Medical Devices, Washington, DC. Institute of Medicine.

NRC (National Research Council). 1990. *Health Effects of Exposure to Low Levels of Ionizing Radiation: BEIR V*. Washington, DC: National Academy Press.

Nussbaum D. 2003. *Cochlear Implants: Navigating a Forest of Information . . . One Tree at a Time*. Washington, DC: Laurent Clerc National Deaf Education Center, Gallaudet University. [Online]. Available: http://clerccenter2.gallaudet.edu/KidsWorldDeafNet/e-docs/CI/CI-E.pdf [accessed July 8, 2005].

O'Neil A, Petersen L, Cook E, Bates D, Lee T, Brennan T. 1993. Physician reporting compared with medical-record review to identify adverse medical events. *Annals of Internal Medicine* 119(5):370–376.

O'Shea JC, Kramer JM, Califf RM, Peterson ED. 2004. Sharing a commitment to improve cardiovascular devices; Part I: Identifying holes in the safety net. *American Heart Journal* 147(6):980.

OIG (Office of Inspector General). 1991. *FDA Medical Device Regulation from Premarket Review to Recall*. Washington, DC: U.S. Department of Health and Human Services. [Online]. Available: http://oig.hhs.gov/oei/reports/oei-09-90-00040.pdf [accessed July 8, 2005].

OIG. 1996. *Postmarketing Studies of Prescription Drugs*. Washington, DC: U.S. Department of Health and Human Services. [Online]. Available: http://oig.hhs.gov/oei/reports/oei-03-94-00760.pdf [accessed July 8, 2005].

Okie S. 2005. What ails the FDA? *New England Journal of Medicine* 352(11):1063–1066.

Omeish A, Hijazi Z. 2001. Transcatheter closure of atrial septal defects in children and adults using the Amplatzer Septal Occluder. *Journal of Interventional Cardiology* 14(1):37–44.

OST (Office of Science and Technology). 2002. *Office of Science and Technology (OST) Annual Report: Fiscal Year 2001*. Washington, DC: U.S. Department of Health and Human Services. [Online]. Available: http://www.fda.gov/cdrh/annual/fy2001/ost/ostfy01.pdf [accessed July 8, 2005].

Ostrov B, Francisco J, Lyons J. 2003 (June 13). Heart device firm pleads guilty to hiding problems. *Mercury News*. Unpaged. [Online]. Available: http://www.siliconvalley.com/mld/siliconvalley/news/local/6078462.htm [accessed March 3, 2005].

OTA (Office of Technology Assessment). 1984. *Federal Policies and the Medical Device Industry*. Washington, DC: OTA. [Online]. Available: http://www.wws.princeton.edu/~ota/disk3/1984/8413_n.html [accessed July 8, 2005].

P000013 (Food and Drug Administration). 2003. Osteonics. *Approved Labeling: ABC System; Trident™ System*. [Online]. Available: http://www.fda.gov/cdrh/pdf/p000013c.html [accessed July 8, 2005].

P000029 (Food and Drug Administration). 2001 (September 24). Letter to Mark M. Yacura, Buchanan Ingersoll P.C. re: Approval of PMA for Deflux® Injectable Gel. [Online]. Available: http://www.fda.gov/cdrh/pdf/p000029a.pdf [accessed July 8, 2005].

P000039 (Food and Drug Administration). 2001a (December 5). Letter to Frank Gougeon, AGA Medical Corporation re: Approval of PMA for AMPLATZER® Septal Occluder (ASO) and the AMPLATZER® Exchange System. [Online]. Available: http://www.fda.gov/cdrh/pdf/P000039a.pdf [accessed July 8, 2005].

P000039 (Food and Drug Administration). 2001b (September 10). AGA Medical Corporation. *Summary of Safety and Effectiveness for AMPLATZER® Septal Occluder (ASO) System*. [Online]. Available: http://www.fda.gov/cdrh/pdf/P000039b.pdf [accessed July 8, 2005].

P000039-S001 (Food and Drug Administration). 2002 (March 27). Letter to AGA Medical Corporation re: Approval of PMA Supplement for the post-approval study protocol for the AMPLATZER® Septal Occluder Device.

P000057 (Food and Drug Administration). 2001. Ascension Orthopedics, Inc. *Approved Patient Labeling: Ascension® MCP*. [Online]. Available: http://www.fda.gov/cdrh/pdf/p000057d.pdf [accessed July 8, 2005].

P000058 (Food and Drug Administration). 2002. Medtronic. *Approved Labeling: InFUSE™ Bone Graft/LT-CAGE™ Lumbar Tapered Fusion Devices*. [Online]. Available: http://www.fda.gov/cdrh/pdf/P000058c.pdf [accessed July 8, 2005].

P020003 (Food and Drug Administration). 2002. Mentor Corporation. *Summary of Safety and Effectiveness Data: Mentor Saline-Filled Testicular Prosthetic*. [Online]. Available: http://www.fda.gov/cdrh/pdf2/P020003b.pdf [accessed July 8, 2005].

P850007-S027 (Food and Drug Administration). 2005. Orthofix, Inc. *Supplemental approval of marketing for the Physio-Stim Models 3202, 3302, 3313, 3314, 3315 and Spinal-Stim Model 2212*. [Online]. Available: http://www.fda.gov/cdrh/pma/pmaapr05.html [accessed July 8, 2005].

P860004-S042 (Food and Drug Administration). 1999 (March 18). Medtronic, Inc. *Supplemental Approval of PMA Supplement for Medtronic Synchromed™ Infusion System*. [Online]. Available: http://www.fda.gov/cdrh/pma/pmamar99.html [accessed July 8, 2005].

P990020 (Food and Drug Administration). 1999 (September 28). Letter to Brian Sheahan, Medtronic re: RMA Approval for AnueRx™ Stent Graft System. [Online]. Available: http://www.fda.gov/cdrh/pdf/P990020a.pdf [accessed July 8, 2005].

Pandey S, Wilson M, Trivedi R, Izak A, Macky T, Werner L, Apple D. 2001. Pediatric cataract surgery and intraocular lens implantation: Current techniques, complications, and management. *International Ophthalmology Clinics* 41(3):175–196.

Peabody J, Gregory G, Willis M, Tooley W. 1978a. Transcutaneous oxygen tension in sick infants. *American Review of Respiratory Disease* 118(1):83–87.

Peabody J, Willis M, Gregory G, Tooley W, Lucey J. 1978b. Clinical limitations and advantages of transcutaneous oxygen electrodes. *Acta Anaesthesiologica Scandinavica. Supplementum* 68:76–82.

Pena C, Bowsher K, Samuels-Reid J. 2004. FDA-approved neurologic devices intended for use in infants, children, and adolescents. *Neurology* 63(7):1163–1167.

Peterson E, Hirshfeld JJ, Ferguson T, Kramer J, Califf R, Kessler L. 2004. Part II: Sealing holes in the safety net. *American Heart Journal* 147(6):985–990.

Phillips P, Less J. 1999. The development of a new 510(k) program. *Medical Device and Diagnostic Industry*. June: Unpaged. [Online]. Available: http://www.devicelink.com/mddi/archive/99/06/019.html [accessed July 8, 2005].

Pocock S. 1993. Statistical and ethical issues in monitoring clinical trials. *Statistics in Medicine* 12(15-16):1459–1469.

Pollack I, Albright A, Adelson P. 1999. A randomized, controlled study of a programmable shunt valve versus a conventional valve for patients with hydrocephalus. Hakim-Medos Investigator Group. *Neurosurgery* 45(6):1399–1411.

Pressly N (for the Center for Devices and Radiological Health). 2003. *FDA Public Health Web Notification: Risk of Bacterial Meningitis in Children with Cochlear Implants*. [Online]. Available: http://www.fda.gov/cdrh/safety/cochlear.pdf [accessed July 8, 2005].

PSU (Pennsylvania State University). 2004. $5 million NIH contract to fund development of pediatric heart assist device. *Penn State Live*. [Online]. Available: http://live.psu.edu/story/6819 [accessed July 8, 2005].

Quinley KM. 2001 (February 12). Risk management and product liability implications of FDA MAUDE reporting. *AdvaMed Business Solutions*. [Online]. Available: http://www.advamed.org/business-solutions/bs-maude.html [accessed July 8, 2005].

Rabkin E, Hoerstrup S, Aikawa M, Mayer J, Schoen F. 2002. Evolution of cell phenotype and extracellular matrix in tissue-engineered heart valves during in-vitro maturation and in-vivo remodeling. *Journal of Heart Valve Disease* 11(3):308–314.

Rados C. 2003. FDA works to reduce preventable medical device injuries. *FDA Consumer Magazine* 37(4): Unpaged. [Online]. Available: http://www.fda.gov/fdac/features/2003/403_devices.html [accessed July 8, 2005].

Rais-Bahrami K, Nunez S, Revenis M, Luban N, Short B. 2004. Follow-up study of adolescents exposed to Di (2-Ethylhexyl) Phthalate (DEHP) as neonates on Extracorporeal Membrane Oxygenation (ECMO) support. *Environmental Health Perspectives* 112(13):1339–1340. [Online]. Available: http://ehp.niehs.nih.gov/docs/2004/6901/abstract.html [accessed July 8, 2005].

Rashkind W. 1971. Palliative procedures for transposition of the great arteries. *British Heart Journal* 33(Suppl):69–72.

Rashkind W. 1983. Balloon atrioseptostomy revisited: The first fifteen years. *International Journal of Cardiology* 4(3):369–372.

Rashkind W, Miller W. 1968. Transposition of the great arteries. Results of palliation by balloon atrioseptostomy in thirty-one infants. *Circulation* 38(3):453–462.

Rashkind W, Waldhausen J, Miller W, Friedman S. 1969. Palliative treatment in tricuspid atresia. Combined balloon atrioseptostomy and surgical alteration of pulmonary blood flow. *Journal of Thoracic and Cardiovascular Surgery* 57(6):812–818.

Ray W, Stein M, Daugherty J, Hall K, Arbogast P, Griffin M. 2002. COX-2 selective non-steroidal anti-inflammatory drugs and risk of serious coronary heart disease. *Lancet* 360(9339):1071–1073.

Reed M, Gal P. 2004. Principles of drug therapy. In: Berhman R, Kliegman R, Jenson H, eds. *Nelson Textbook of Pediatrics*. 17th ed. Philadelphia, PA: WB Sanders. Pp. 2427–2431.

Reefhuis J, Honein M, Whitney C, Chamany S, Mann EA, Biernath KR, Broder K, Manning S, Avashia S, Victor M, Costa P, Devine O, Graham A, Boyle C. 2003. Risk of bacterial meningitis in children with cochlear implants. *New England Journal of Medicine* 349(5):435–445.

Rennie D. 2004. Trial registration: A great idea switches from ignored to irresistible. *Journal of the American Medical Association* 292(11):1359–1362.

Rhees D, Jeffrey K. 2000. Earl Bakken's little white box: The complex meanings of the first transistorized pacemaker. In: Finn B, ed. *Exposing Electronics*. London: Harwood. Pp. 75–113.

Richwine L. 2004 (November 18). Congress told FDA failed public on Vioxx. *Reuters*. Unpaged. [Online]. Available: http://www.commondreams.org/headlines04/1118-09.htm.

Rolison MR, Scherman A. 2002. Factors influencing adolescents' decisions to engage in risk-taking behavior. *Adolescence* 37(147):585–596.

Ross M, Fresquez M, El-Haddad M. 2000. Impact of FDA advisory on reported vacuum-assisted delivery and morbidity. *Journal of Maternal-Fetal Medicine* 9(6):321–326.

Rundles, MC. 2004. *What's New: AHRQ Plans Additional CERTs Centers for 2005*. [Online]. Available: http://www.certs.hhs.gov/whats_new/archive/2004/20041222_01.html [accessed July 8, 2005].

Samore M, Evans R, Lassen A, Gould P, Lloyd J, Gardner R, Abouzelof R, Taylor C, Woodbury D, Willy M, Bright R. 2004. Surveillance of medical device-related hazards and adverse events in hospitalized patients. *Journal of the American Medical Association* 291(3):325–334.

Samson R, Berg R, Bingham R, Biarent D, Coovadia A, Hazinski M, Hickey R, Nadkarni V, Nichol G, Tibballs J, Reis A, Tse S, Zideman D, Potts J, Uzark K, Atkins D, Pediatric Advanced Life Support Task Force, International Liaison Committee on Resuscitation. 2003. Use of automated external defibrillators for children: An update: An advisory statement from the pediatric advanced life support task force, International Liaison Committee on Resuscitation. *Circulation* 107(25):3250–3255.

Samuels R, Jones M. 1994. Orthodontic facebow injuries and safety equipment. *European Journal of Orthodontics* 16(5):385–394.

Samuels R, Willner F, Knox J, Jones M. 1996. A national survey of orthodontic facebow injuries in the UK and Eire. *British Journal of Orthodontics* 23(1):11–20.

Sansom W. 2004. Reinventing the rib. *The Mission* November/December: Unpaged. [Online]. Available: http://www.uthscsa.edu/mission/article.asp?id=283 [accessed July 8, 2005].

Sawyer D (for Center for Devices and Radiological Health). 1996. *Do It By Design: An Introduction to Human Factors in Medical Devices*. Rockville, MD: FDA. [Online]. Available: http://www.fda.gov/cdrh/humfac/doitpdf.pdf [accessed July 8, 2005].

Schaff H, Danielson G. 1986. Current status of valve replacement in children. *Cardiovascular Clinics* 16(2):427–436.

Schiller J, Coriaty-Nelson Z, Barnes P. 2004. *Early Release of Selected Estimates Based on Data from the 2003 National Health Interview Survey*. Hyattsville, MD: National Center for Health Statistics. [Online]. Available: http://www.cdc.gov/nchs/about/major/nhis/released200406.htm [accessed July 8, 2005].

Schillinger D. 2004 (March). Lethal cap. *Morbidity and Mortality Rounds on the Web*. Unpaged. [Online]. Available: http://www.webmm.ahrq.gov/case.aspx?caseID=53 [accessed July 8, 2005].

Schultz DG (for Center for Devices and Radiological Health). 2004 (August 27). Letter to CDRH Senior Management Team re: Identification, Management, and Resolution of Postmarket Safety Issues.

Secunda J (for AdvaMed). 2005 (May 2). Letter to Daniel G. Shultz (of the Center for Devices and Radiological Health) re: Results of AdvaMed Survey to Evaluate the Status of Condition of Approval Studies.

Shaffer K, Mullins C, Grifka R, O'Laughlin M, McMahon W, Ing F, Nihill M. 1998. Intravascular stents in congenital heart disease: Short- and long-term results from a large single-center experience. *Journal of the American College of Cardiology* 31(3):661–667.

Shatin D, Bright RA, Astor B. In Press. Databases for studying the epidemiology of implanted medical devices. In: Johnson FE, Virgo KS, eds. *The Bionic Human: Health Promotion for People with Implanted Prosthetic Devices*. Totowa, NJ: Humana Press.

Shea K (for AAP Committee on Environmental Health). 2003. Technical Report: Pediatric Exposure and Potential Toxicity of Phthalate Plasticizers. *Pediatrics* 111(6):1467–1474.

Shirkey H. 1968. Editorial comment: Therapeutic orphans. *Journal of Pediatrics* 72(1):119–120.

Silka M, Kron J, Dunnigan A, Dick M. 1993. Sudden cardiac death and the use of implantable cardioverter-defibrillators in pediatric patients. The Pediatric Electrophysiology Society. *Circulation* 87(3):800–807.

Simpser E. 2004 Statement for the Committee on Postmarket Surveillance of Pediatric Medical Devices, Washington, DC. Institute of Medicine.

Slonim AD, LaFleur BJ, Ahmed W, Joseph JG. 2003. Hospital-reported medical errors in children. *Pediatrics* 111(3):617–621.

Smith E, Butler W, Barker F. 2004. In-hospital mortality rates after ventriculoperitoneal shunt procedures in the United States, 1998 to 2000: Relation to hospital and surgeon volume of care. *Journal of Neurosurgery: Spine* 100(2):90–97.

Solomon M, McLeod R. 1995. Should we be performing more randomized controlled trials evaluating surgical operations? *Surgery* 118(3):459–467.

Srinivasan A, Wolfenden L, Song X, Mackie K, Hartsell T, Jones H, Diette G, Orens J, Yung R, Ross T, Merz W, Scheel P, Haponik E, Perl T. 2003. An outbreak of Pseudomonas aeruginosa infections associated with flexible bronchoscopes. *New England Journal of Medicine* 348(3):221–227.

Srinivasan A, Wolfenden L, Song X, Perl T, Haponik E. 2004. Bronchoscope reprocessing and infection prevention and control: Bronchoscopy-specific guidelines are needed. *Chest* 125(1):307–314.

Staal M, Meihuizen-de Regt M, Hess J. 1997. The long-term outlook for hydrocephalus in childhood. A ten-year cohort study of 155 patients. *Pediatric Neurosurgery* 27(2):63–70.

Statz-Hill M. 2004. Comments to the Committee on Postmarket Surveillance of Pediatric Medical Devices, Washington, DC. Institute of Medicine.

Steinberg L. 2004. Risk taking in adolescence: What changes, and why? *Annals of the New York Academy of Sciences* 1021(Jun):51–58.

Steinbrook R. 2002. Testing medications in children. *New England Journal of Medicine* 110(2):364–370.

Steinbrook R. 2004. Public registration of clinical trials. *New England Journal of Medicine* 351(4):315–317.

Stock U, Vacanti J, Mayer Jr. J, Wahlers T. 2002. Tissue engineering of heart valves—current aspects. *Thoracic and Cardiovascular Surgeon* 50(3):184–193.

STROBE (Strengthening the Reporting of Observational studies in Epidemiology). 2005. *STROBE Statement*. [Online]. Available: http://www.strobe-statement.org/1513.html [accessed July 8, 2005].

Study Group on Medical Devices (Cooper Committee). 1970. Department of Health, Education and Welfare. *Medical Devices: A Legislative Plan*. Washington, DC: Department of Health, Education and Welfare.

Suresh G, Horbar JD, Plsek P, Gray J, Edwards WH, Shiono PH, Ursprung R, Nickerson J, Lucey JF, Goldmann D, for the NICQ2000 and NICQ2002 investigators of the Vermont Oxford Network. 2004. Voluntary anonymous reporting of medical errors for neonatal intensive care. *Pediatrics* 113(6):1609–1618.

Swann JP. 1999. The 1941 sulfathiazole disaster and the birth of good manufacturing practices. *PDA Journal of Pharmaceutical Science and Technology* 53(3):148–153.

Theodorou A, Gutierrez J, Berg R. 2003. Fire attributable to a defibrillation attempt in a neonate. *Pediatrics* 112(3 Pt 1):677–679.

Thomson J, Aburawi E, Watterson K, Van Doorn C, Gibbs J. 2002. Surgical and transctheter (Amplatzer) closure of atrial septal defects: A prospective comparison of results and cost. *Heart* 87(5):466–469.

Tillman D-B (for Food and Drug Administration). 2002 (May 17). Letter to Collins Medical, Inc. re: 510(k) Approval for Infant Plethysmograph Model 004400.

Tillman D-B, Gardner S (for Food and Drug Administration). 2004 (September 27). Letter to Institute of Medicine re: FDA's Responses to the May 12, 2004, Questions Sent to Dr. Daniel Schultz, Acting Commissioner, Regarding Commitments for Postmarket Studies.

Tilson H. 1992. Pharmacosurveillance: Public health monitoring of medication. In: Halperin W, Baker E, Monson R, eds. *Public Health Surveillance*. New York, NY: Van Nostrand Reinhold. Pp. 206–229.

Todd J, Ruhl C, Gross T. 1997a. Injury and death associated with hospital bed side-rails: Reports to the US Food and Drug Administration from 1985 to 1995. *American Journal of Public Health* 87(10):1675–1677.

Todd J, Ruhl C, Gross T. 1997b. Injury and death associated with hospital bed side-rails: Reports to the US Food and Drug Administration from 1985 to 1995 (Erratum). *American Journal of Public Health* 87(12):2052.

Townsend D, Hoffinger S. 2000. Intramedullary nailing of femoral shaft fractures in children via the trochanter tip. *Clinical Orthopaedics and Related Research* 376:113–118.

Truog RD. 1999. Informed consent and research design in critical care medicine. *Critical Care* 3(3):R29–R33.

Truog WE. 1998. Inhaled nitric oxide: A tenth anniversary observation. *Pediatrics* 101(4 Pt 1):696–697.

Tucker A. 2004. A case study of operational failure in home healthcare. *Journal for Healthcare Quality* 26(3):38–43.

Tunis S, Stryer D, Clancy C. 2003. Practical clinical trials: Increasing the value of clinical research for decision making in clinical and health policy. *Journal of the American Medical Association* 290(12):1624–1632.

Tyco. 2004 (August 26). *Nellcor Announces Nationwide Voluntary Recall of All Capno-Probe™ Sublingual Sensors*. [Online]. Available: http://www.tyco.com/tyco/press_release_detail.asp?prid=732 [accessed July 8, 2005].

UK Collaborative ECMO Group. 1998. The Collaborative UK ECMO Trial: Follow-up to 1 year of age. *Pediatrics* 101(4):e1.

United States v. Bacto-Unidisk (*United States v. An Article of Drug . . . Bacto-Unidisk. . . . Certiorari to the United Stated Court of Appeals for the Sixth Circuit*). 1969. 394 U.S. 784.

University of Michigan. 2005. *ELSO (Extracorporeal Life Support Organization) Registry*. [Online]. Available: http://www.med.umich.edu/ecmo/registry.htm [accessed July 8, 2005].

U.S. Congress (House Committee on Interstate and Foreign Commerce). 1973 (October 23–24). *Medical Devices, Hearing before the Subcommittee on Public Health and the Environment*. Washington, DC: U.S. Government Printing Office.

Vedantam S. 2004 (August 10). FDA study confirms antidepressant risks: Drugs linked to more suicides among children, unpublished analysis says. *Washington Post*. P. A6.

Vidailhet M, Vercueil L, Houeto J-L, Krystkowiak P, Benabid A-L, Cornu P, Lagrange C, Tézenas du Montcel S, Dormont D, Grand S, Blond S, Detante O, Pillon B, Ardouin C, Agid Y, Destée A, Pollak P, the French Stimulation du Pallidum Interne dans la Dystonie (SPIDY) Study Group. 2005. Bilateral Deep-Brain Stimulation of the Globus Pallidus in Primary Generalized Dystonia. *New England Journal of Medicine* 352(5):459–467.

Wald H, Shojania KG. 2001a. Incident Reporting. In: Markowitz AJ, ed. *Making Health Care Safer: A Critical Analysis of Patient Safety Practices Evidence Report/Technology Assessment*. Vol. 4. Rockville, MD: AHRQ. [Online]. Available: http://www.ncbi.nlm.nih.gov/books/bv.fcgi?rid=hstat1.section. 59490 [accessed July 8, 2005].

Wald H, Shojania KG. 2001b. Root cause analysis. In: Markowitz AJ, ed. *Making Health Care Safer: A Critical Analysis of Patient Safety Practices Evidence Report/Technology Assessment*. Vol. 43. Rockville, MD: AHRQ. [Online]. Available: http://www.ahrq.gov/clinic/ptsafety/chap5.htm [accessed July 8, 2005].

Waltzman S, Cohen N, Green J, Roland JJ. 2002. Long-term effects of cochlear implants in children. *Otolaryngology—Head & Neck Surgery* 126(5):505–511.

Warnes C, Liberthson R, Danielson JGK, Dore A, Harris L, Hoffman JIE, Somerville J, Williams R, Webb G. 2001. 32nd Bethesda Conference: Care of the adult with congenital heart disease. Task force 1: The changing profile of congenital heart disease in adult life. Bethesda, MD: The American College of Cardiology. In: *Journal of the American College of Cardiology* 37(5):1170–1175. [Online]. Available: http://www.acc.org/clinical/bethesda/beth32/task1.htm [accessed July 8, 2005].

Whitmore E. 2004. It's not your father's FDA: The "modernization" of medical product regulation. In: *Development of FDA-Regulated Products: Prescription Drugs, Biologics, and Medical Devices*. Milwaukee, WS: ASQ Quality Press. Pp. 11–32.

WHO (World Health Organization). 2003. *Medical Device Regulations: Global Overview and Guiding Principles*. Geneva, Switzerland: WHO. [Online]. Available: http://www.who.int/medical_devices/publications/en/MD_Regulations.pdf [accessed July 8, 2005].

Wiklund M. 2003 (January). Human factors: Is your human factors program ready for FDA scrutiny? *Medical Device and Diagnostic Industry*. Unpaged. [Online]. Available: http://www.devicelink.com/mddi/archive/03/01/004.html [accessed July 8, 2005].

Wilson A, Gardner M, Armstrong M, Folck B, Escobar G. 2000. Neonatal assisted ventilation: Predictors, frequency, and duration in a mature managed care organization. *Pediatrics* 105(4 Pt 1):822–830.

Wright Medical Technology, Inc. 2004. *What is REPIPHYSIS® Expandable Technology?* [Online]. Available: http://www.wmt.com/expandableimplant/Patients/trepiphysis.asp [accessed July 8, 2005].

WTTG. 2004 (November 5). *Investigative Report: Headgear Hazard, WTTG Fox 5 News*. [Online]. Available: http://www.fox5dc.com/_ezpost/data/9607.shtml [accessed July 8, 2005].

Zanchetta M, Maiolino P. 2004. Intracardiac echocardiography. Do we need a new ultrasonographic window? *Italian Heart Journal* 5(3):173–177. [Online]. Available: http://www.italheartj.org/pdf_files/20040083.pdf [accessed July 8, 2005].

Zarins C, Bloch D. 2004. Misperceptions regarding the long-term safety of the AneuRx stent graft. *Journal of Vascular Surgery* 40(3):594–595. [Online]. Available: http://vascular.stanford.edu/faculty/zarins_pdf/2004/ltr_zarins_jvs0904.pdf [accessed July 8, 2005].

Zhou W, Pool V, Iskander J, English-Bullard R, Ball R, Wise R, Haber P, Pless R, Mootrey G, Ellenberg S, Braun M, Chen R. 2003. Surveillance for safety after immunization: Vaccine adverse event reporting system (VAERS)—United States, 1991–2001. *Morbidity and Mortality Weekly Report* 52(SS-1):1–10. [Online]. Available: http://www.cdc.gov/mmwr/PDF/ss/ss5201.pdf [accessed July 8, 2005].

Appendixes

A

Study Origins and Activities

The Medical Device User Fee and Modernization Act of 2002 (P.L. 107–250) called for the Institute of Medicine (IOM) to conduct a study of postmarket surveillance of pediatric medical devices. IOM appointed a committee of 13 experts to oversee the study. Its task was to develop a report that specifically examined the system under the Federal Food, Drug, and Cosmetic Act for postmarket surveillance of medical devices to assess whether the system as administered by the U.S. Food and Drug Administration provides adequate safeguards for the use of devices in children. As called for in the legislation, the study committee assessed

- the U.S. Food and Drug Administration's monitoring and use of adverse reaction reports, registries, clinical studies, and other postmarket surveillance activities to identify unsafe or ineffective products;
- the adequacy of the agency's monitoring of commitments for further clinical studies made by manufacturers at the time of approval of specific medical devices;
- the adequacy of postmarket surveillance studies to evaluate how children's active lifestyles may affect implant failure rates and longevity; and
- the length of studies, including whether they continue long enough to evaluate the impact of children's growth and development given the expected length of time that a child will have an implant.

The committee met five times between April 2004 and March 2005. It organized two advisory panels to provide additional technical guidance on clinical and technical issues. It commissioned two background papers. The

committee conducted three meetings with public sessions, including one to hear the views of family support and advocacy organizations and health care groups (with written statements invited from additional organizations). The committee also met with parents and young people who had personal experiences with implants or other complex medical devices. The agendas and participants for the public meetings are listed below.

INSTITUTE OF MEDICINE
Committee on Postmarket Surveillance of Pediatric Medical Devices
Room 204, The Keck Center, National Academy of Sciences
500 Fifth Street NW, Washington, DC
Public Session—April 15, 2004

1:00 **Welcome and introductions**

1:10 **FDA Context and Perspectives**

Donna-Bea Tillman, Ph.D.
Deputy Director, Office of Device Evaluation
Center for Devices and Radiological Health
U.S. Food and Drug Administration
Rockville, MD

Thomas Gross, M.D.
Director, Division of Postmarket Surveillance
Center for Devices and Radiological Health
U.S. Food and Drug Administration
Rockville, MD

2:40 **Break**

3:00 **Research on Postmarket Surveillance: Experience of Duke Center for Education and Research on Therapeutics**

Judith M. Kramer, M.D.
Principal Investigator, Duke Center for Education and Research on Therapeutics
Duke University Medical Center
Durham, NC

4:00 **Analysis of FDA Adverse Event Reports**

Mark Bruley, B.Sc.
Vice President, ECRI
Plymouth Meeting, PA

5:15 **Adjourn**

* * *

INSTITUTE OF MEDICINE
Committee on Postmarket Surveillance of Pediatric Medical Devices
Room 100, The Keck Center, National Academy of Sciences
500 Fifth Street NW, Washington, DC
Public Session—June 24, 2004

1:00 Welcome and introductions

1:10 Update from CDRH/FDA: Thomas Gross, M.D.

Briefing on Legislative Interest in Pediatric Medical Devices: Vipul Mankad, M.D. (Robert Wood Johnson Foundation fellow with Senate Health, Education, Labor and Pensions Committee)

1:30 Discussion with Clinical Advisory Panel

Jonathan Abramson, M.D.
Professor and Chair, Department of Pediatrics
Wake Forest University
Winston Salem, NC

Francis Sessions Cole, III, M.D.
Vice Chair and Park J. White Professor of Pediatrics
Washington University School of Medicine
Director, Division of Newborn Medicine
St. Louis Children's Hospital
St. Louis, MO

Barbara Fivush, M.D.
Professor of Pediatrics
Johns Hopkins School of Medicine
Division Chief, Pediatric Nephrology
Johns Hopkins Hospital
Baltimore, MD

Susan T. Iannaccone, M.D., F.A.A.N.
Director, Neuromuscular Disease and Neurorehabilitation
Texas Scottish Rite Hospital for Children
Professor of Neurology
UT Southwestern Medical Center
Dallas, TX

John K. Niparko, M.D.
George T. Nager Professor
Director, Division of Otology, Neurotology & Skull Base Surgery
Johns Hopkins School of Medicine
Baltimore, MD

Ramon L. Ruiz, D.M.D., M.D.
Assistant Professor, Oral/Maxillofacial Surgery & Pediatrics
University of North Carolina at Chapel Hill
Director, Pediatric Oral/Maxillofacial Surgery
North Carolina Children's Hospital
Chapel Hill, NC

Frederick J. Schoen, M.D., Ph.D.
Professor of Pathology and Health Sciences and Technology
Harvard Medical School
Executive Vice Chairman, Department of Pathology
Brigham and Women's Hospital
Boston, MA

3:45 Break

4:00 Discussion with Methods Advisory Panel

Elizabeth B. Andrews, Ph.D., M.P.H.
Vice President
Pharmacoepidemiology and Risk Management
RTI Health Solutions
Research Triangle Park, NC

Roselie A. Bright, Sc.D.
Epidemiologist
Division of Postmarket Surveillance
Office of Surveillance and Biometrics
Center for Devices and Radiological Health
U.S. Food and Drug Administration
Rockville, MD

Robert T. Chen, M.D., M.A.
Chief, Immunization Safety Branch
National Immunization Program
Centers for Disease Control and Prevention
Atlanta, GA

Harry A. Guess, M.D., Ph.D.
Professor of Epidemiology
School of Public Health
University of North Carolina at Chapel Hill
Chapel Hill, NC

5:30 Adjourn

* * *

INSTITUTE OF MEDICINE
Committee on Postmarket Surveillance of Pediatric Medical Devices
Lecture Room, National Academy of Sciences
2101 Constitution Avenue, NW, Washington, DC
Public Session—August 31, 2004

8:20 **Welcome**

8:30 **Advanced Medical Technology Association**

Susan Alpert, M.D.
Vice President, Chief Quality and Regulatory Officer
Medtronic
Minneapolis, MN

9:00 **American College of Cardiology, Congenital Heart Disease and Pediatric Cardiology Committee**

Mark Boucek, M.D.
Director of Pediatric Heart Failure and Transplant Research Programs
The Children's Hospital Denver
University of Colorado School of Medicine
Denver, CO

Pediatric Section, American Thoracic Society

Ann C. Halbower, M.D.
Assistant Professor of Pediatrics and Medical Director of Pediatric Sleep Disorders Program
Johns Hopkins University
Baltimore, MD

9:45 **American Academy of Pediatrics**

Jon Abramson, M.D.
Weston L. Kelsey Chair of Pediatrics
Wake Forest University Baptist Medical Center
Winston-Salem, NC

Pediatric Orthopedic Society of North America
Michael Vitale, M.D., M.P.H.
Chair, Evidence Analysis Work Group and Assistant Professor in the Division of Pediatric Orthopaedic Surgery Columbia University
New York, NY

10:30 **Break**

10:50 National Association of Children's Hospitals and Related Institutions[1]

Joelle Mast, M.D., Ph.D.
Chief Medical Officer and Chief of Pediatrics
Blythedale Children's Hospital
Valhalla, NY

Edwin Simpser, M.D.
Executive Vice President and Chief Medical Officer
St. Mary's Hospital for Children
Assistant Professor of Clinical Pediatrics
New York University School of Medicine
New York, NY

11:30 National Consumers League
Alison Rein
Assistant Director, Food and Health Policy
Washington, DC

12:00 Adjourn

NOTE: The following organizations endorsed the statement of the American Academy of Pediatrics: Ambulatory Pediatric Association, American Pediatric Society, Association of Medical School Pediatric Department Chairs, Society for Pediatric Research. Additional written statements were provided by: Section on Neurological Surgery (of the American Academy of Pediatrics); Society for Pediatric Anesthesia; American Pediatric Surgical Association; and Anthony D. Slonim, M.D., M.P.H. (of Children's National Medical Center, Washington, DC).

* * *

INSTITUTE OF MEDICINE
Committee on Postmarket Surveillance of Pediatric Medical Devices
Lecture Room, National Academy of Sciences
2101 Constitution Avenue, NW, Washington, DC
Public Session—August 31, 2004 (afternoon)
Meeting with Families

Wendy Baskins
Nancy Harder and Ben Harder

[1]Statements are those of guest speakers who represent member hospitals of NACHRI but who are not speaking for NACHRI.

Donya Hartley
Melisande Statz-Hill and Benjamin Hill
Penny Hill and Amanda Hill
Kim L. Katka
Karen Marston

B

Medical Devices for Pediatric Care[1]

PART I: DEVICES OTHER THAN IMPLANTS

This list includes medical devices—other than implants—that are typically used in the clinical specialty of pediatrics and are not generic in nature. That is, most are either used uniquely or nearly uniquely with children or are manufactured in special sizes for use with children.

1. Adhesive Strips, Butterfly [10-278]
2. Adhesive Strips, General-Purpose [16-769]
3. Adhesive Strips, Hypoallergenic [10-028]
4. Adhesive Strips, Waterproof [10-029]
5. Airways, Nasopharyngeal [10-057]
6. Alarms, Enuresis [11-588]
7. Analyzers, Physiologic, Middle Ear [15-634]
8. Analyzers, Physiologic, Middle Ear, Acoustic Reflectometry [18-784]

[1]SOURCE: ECRI's Health Devices International Sourcebase (http://www.ecri.org/Products_and_Services/Products/Health_Devices International_Sourcebase/Default.aspx). Device terms and coding numbers are from ECRI's *Universal Medical Device Nomenclature System* (UMDNS) and are copyrighted by ECRI. (See http://www.ecri.org/Products_and_Services/Products/UMDNS/Default.aspx.) The ECRI *Health Devices International Sourcebase* includes device definitions for approximately 75 percent of these terms. Definitions for the remainder are being drafted.

9. Analyzers, Physiologic, Middle Ear, Impedance Tympanometry [18-783]
10. Analyzers, Physiologic, Pulmonary Function, Neonatal/Pediatric [17-699]
11. Analyzers, Point-of-Care, Whole Blood, Glycated Hemoglobin [20-385]
12. Analyzers, Point-of-Care, Whole Blood/Urine, Multianalyte, Diabetes [20-386]
13. Anoscopes [10-156]
14. Aprons, Infant Evacuation [20-466]
15. Aspirators, Infant [10-214]
16. Aspirators, Nasal [10-216]
17. Auditory Function Screening Devices [17-601]
18. Auditory Function Screening Devices, Newborn [20-167]
19. Bassinets [10-302]
20. Batteries, Implantable Device [18-554]
21. Beds, Fixed, Cradle [10-328]
22. Beds, Fixed, Cradle, Pediatric [10-362]
23. Beds, Fixed, Flotation Therapy, Neonatal [16-168]
24. Beds, Fixed, Neonatal [18-397]
25. Beds, Mechanical, Neonatal [18-393]
26. Beds, Mechanical, Pediatric [18-392]
27. Belts, Electrode [16-226]
28. Bilirubinometers, Cutaneous [16-166]
29. Blankets, Circulating-Fluid [12-067]
30. Blankets, Forced-Air [18-852]
31. Blankets, Infant [10-417]
32. Bottles, Infant Nursing [12-779]
33. Bronchoscopes [10-491]
34. Bronchoscopes, Flexible [15-073]
35. Bronchoscopes, Flexible, Video [17-662]
36. Bronchoscopes, Rigid [15-074]
37. Cannulae, Nasal, Continuous Positive Airway Pressure [12-701]
38. Cannulae, Nasal, Oxygen Supply [12-700]
39. Cannulae, Tracheostomy [14-089]
40. Caps, Infant [17-142]
41. Catheter Introducers-Hemostasis Valve [17-578]
42. Catheterization Kits, Intravenous [12-161]
43. Catheters, Cardiac, Flotation Balloon [10-700]
44. Catheters, Cardiac, Microflow [18-682]
45. Catheters, Tracheal [18-725]
46. Catheters, Tracheal, Suction [10-749]
47. Catheters, Urinary, Urethral [10-762]

48. Catheters, Vascular, Microflow [10-691]
49. Catheters, Vascular, Umbilical [10-759]
50. Catheters, Vascular, Umbilical, Arterial [18-666]
51. Catheters, Vascular, Umbilical, Central Venous [18-665]
52. Catheters, Wound, Drainage [18-756]
53. Catheters, Wound, Drainage, Suction [18-757]
54. Catheters, Wound, Irrigation [18-758]
55. Chairs, Disabled Patient, Pediatric [10-797]
56. Circumcision Trays, Disposable [10-859]
57. Circumcision Trays, Reusable [10-860]
58. Clamps, Circumcision [10-869]
59. Clamps, Umbilical [10-876]
60. Colonoscopes [10-950]
61. Colonoscopes, Video [17-665]
62. Combs, Lice [17-552]
63. Cradles, Rocking, Computer-Controlled [17-798]
64. Crib Tops [11-049]
65. Cuffs, Blood Pressure [11-073]
66. Cuffs, Tracheostomy Tube [14-094]
67. Cystoscopes [11-112]
68. Cystoscopes, Flexible [17-144]
69. Cystoscopes, Rigid [17-145]
70. Cystourethroscopes [11-114]
71. Diapers, Pediatric [11-240]
72. Droppers, Ear [11-370]
73. Duodenoscopes [11-359]
74. Duodenoscopes, Video [17-654]
75. Electrodes, Electrocardiographic, Neonatal [17-460]
76. Electrodes, Fetal Scalp [11-447]
77. Electrodes, Nasopharyngeal [11-452]
78. Electrodes, Sweat Test [11-461]
79. Endoscopes, Gastrointestinal Tract, Lower Tract [20-479]
80. Endoscopes, Gastrointestinal Tract, Upper Tract [20-478]
81. Endoscopes, Respiratory Tract [20-476]
82. Endoscopes, Urinary Tract [20-483]
83. Enema Bags [11-581]
84. Enema Kits [11-582]
85. Enema Tips [11-583]
86. Enteroscopes [18-125]
87. Enteroscopes, Video [18-126]
88. Exchange Transfusion Kits [11-618]
89. Gastroduodenoscopes [11-853]
90. Gastroscopes [11-856]

91. Gastroscopes, Flexible [11-857]
92. Gastroscopes, Flexible, Video [17-663]
93. Gastroscopes, Rigid [11-858]
94. Hoods, Oxygen [12-027]
95. Humidifiers, Heated [12-050]
96. Humidifiers, Nonheated [12-051]
97. Identification Bracelets [12-088]
98. Immobilizers, Infant [12-097]
99. Incubator/Radiant Warming Units, Infant, Mobile [18-857]
100. Incubators, Infant, Mobile [17-432]
101. Incubators, Infant, Transport [12-114]
102. Infant Care Kits [10-243]
103. Infant Scale Liners [17-653]
104. Intravenous Administration Sets, Scalp Vein [17-825]
105. Iontophoresis Units, Drug Delivery [18-155]
106. Iontophoresis Units, Sweat Test [15-128]
107. Lancets, Blood, Automated [16-380]
108. Laparoscopes [12-291]
109. Laparoscopes, Diagnostic [20-484]
110. Laparoscopes, Surgery [20-485]
111. Laryngoscopes [12-293]
112. Laryngoscopes, Flexible [15-075]
113. Laryngoscopes, Flexible, Intubation [16-331]
114. Laryngoscopes, Rigid [15-076]
115. Laryngostroboscopes [12-294]
116. Lavage Units, Gastric [17-189]
117. Ligators, Umbilical [15-041]
118. Lumbar Puncture Kits [12-404]
119. Manometer Sets, Cerebrospinal Fluid [13-107]
120. Manometer Sets, Venous, Central/Peripheral [10-776]
121. Masks, Resuscitator [17-170]
122. Mitts, Patient [12-559]
123. Monitors, Bedside, Blood Gas, Transcutaneous [17-996]
124. Monitors, Bedside, Blood Gas/pH, Extracorporeal [17-680]
125. Monitors, Bedside, Blood Gas/pH, Intravascular [20-176]
126. Monitors, Bedside, Electrocardiography [12-599]
127. Monitors, Bedside, Physiologic, Neonatal [15-791]
128. Monitors, Bedside, Respiration [12-662]
129. Monitors, Bedside, Respiration, Apnea [12-575]
130. Monitors, Bedside, Respiration, Carbon Dioxide/Oxygen [17-444]
131. Monitors, Bedside, Respiration, Exhaled Carbon Dioxide [16-938]
132. Monitors, Bedside, Respiration, Ventilation/Apnea [12-678]
133. Monitors, Bedside, Temperature [14-034]

134. Nasopharyngoscopes [12-709]
135. Nasoscopes [12-710]
136. Nebulizers, Heated [12-716]
137. Nebulizers, Ultrasonic [12-719]
138. Needles, Injection, Intravenous, Scalp-Vein/Pediatric [12-752]
139. Nephroscopes [15-591]
140. Nephroscopes, Flexible [15-289]
141. Nephroscopes, Rigid [15-290]
142. Nipples, Nursing Bottle [16-761]
143. Nitric Oxide Delivery Units [18-586]
144. Occluders, Cardiac Septum [20-414]
145. Occluders, Umbilical Cord [20-416]
146. Occluders, Vascular [17-731]
147. Occluders, Vascular, Intravascular Embolization [15-034]
148. Occluders, Vascular, Intravascular Embolization, Particulate [20-412]
149. Ophthalmoscope/Otoscopes [18-595]
150. Oral Feeding Kits, Infant [17-486]
151. Orthoses, Head [18-565]
152. Orthoses, Leg [17-859]
153. Otoscopes [12-849]
154. Otoscopes, Pneumatic [18-785]
155. Oximeters, Cerebral [17-942]
156. Oximeters, in Vitro, Point-of-Care [18-635]
157. Oximeters, Pulse [17-148]
158. Oxygenators, Extracorporeal Membrane [17-643]
159. Oxygenators, Intravascular Membrane [18-133]
160. Pacifiers, Infant, Oral [17-512]
161. Pelvimeters [12-980]
162. Percussion Pads [12-935]
163. Percussors [12-986]
164. Perforators, Ear Lobe [12-991]
165. Pharyngoscopes [13-011]
166. Phototherapy Units, Visible Light, Hyperbilirubinemia [17-515]
167. Plates, Dental [20-331]
168. Power Kits, Wheelchair [17-952]
169. Pressure Measuring Units, Esophageal [13-108]
170. Pressure Measuring Units, Inspiratory [13-109]
171. Pressure Measuring Units, Intracranial [13-110]
172. Probes, Eye, Lacrimal [13-120]
173. Probes, Oximeter [17-594]
174. Probes, Thermometer [13-125]
175. Proctoscopes [13-126]

176. Proctosigmoidoscopes [13-127]
177. Protectors, Palatal [17-689]
178. Radiometers, Phototherapy [13-278]
179. Refrigerators, Food, Milk Formula [15-923]
180. Resectoscopes [13-335]
181. Resectoscopes, Urological [18-187]
182. Restraints, Crib [13-351]
183. Sampling Kits, Blood, Fetal Scalp [16-873]
184. Scales, Infant [13-462]
185. Scales, Infant, Warmer/Incubator [18-463]
186. Scissors, Pediatric [13-499]
187. Shields, Heat Loss, Infant [15-752]
188. Shunt Adapters [13-584]
189. Sigmoidoscopes [13-594]
190. Sigmoidoscopes, Flexible [15-057]
191. Sigmoidoscopes, Flexible, Video [17-664]
192. Sigmoidoscopes, Rigid [15-058]
193. Specula, Aural [13-662]
194. Specula, Nasal [13-664]
195. Specula, Ocular [13-663]
196. Specula, Phayrngeal [20-489]
197. Specula, Rectal [13-665]
198. Sphygmomanometers, Electronic, Automatic [16-173]
199. Sphygmomanometers, Electronic, Automatic, Auscultatory [18-325]
200. Sphygmomanometers, Electronic, Automatic, Differential Sensor [18-327]
201. Sphygmomanometers, Electronic, Automatic, Oscillometric [18-326]
202. Sphygmomanometers, Electronic, Manual [16-174]
203. Sphygmomanometers, Aneroid [16-156]
204. Sphygmomanometers, Mercury [16-158]
205. Stimulators, Electrical, Neuromuscular, Gait, Implantable [18-478]
206. Stimulators, Electrical, Neuromuscular, Grasp [18-475]
207. Stimulators, Electrical, Neuromuscular, Scoliosis [17-240]
208. Strollers [18-139]
209. Syringes, Bulb [20-311]
210. Syringes, Plunger, Oral Medication [20-469]
211. Tapes, Umbilical [13-983]
212. Tents, Mist [12-554]
213. Tents, Mist, Face [12-557]
214. Thermometer Kits [14-025]
215. Thermometers, Electronic, Infrared, Ear [17-887]
216. Thermometers, Electronic, Infrared, Skin [17-888]
217. Thermometers, Liquid Crystal [18-302]

218. Thermometers, Mercury, Axillary [18-297]
219. Thermometers, Mercury, Oral [18-295]
220. Thermometers, Mercury, Rectal [18-296]
221. Timers, Apgar Scoring [15-648]
222. Tracheal Tube Adapters [14-080]
223. Tracheal Tube Introducers [17-694]
224. Tracheostomy Care Kits [14-090]
225. Tracheostomy Tube Adapters [14-092]
226. Tracheotomy Kits [14-099]
227. Transilluminators [14-130]
228. Trusses, Infant [14-171]
229. Tubes, Enema [14-194]
230. Tubes, Gastrostomy, Percutaneous Endoscopic [17-790]
231. Tubes, Gastrostomy/Jejunal, Percutaneous Endoscopic [18-764]
232. Tubes, Jejunostomy [18-854]
233. Tubes, Jejunostomy, Percutaneous Endoscopic [17-791]
234. Tubes, Tracheal [14-085]
235. Tubes, Tracheostomy [14-096]
236. Ureterorenoscopes [17-690]
237. Ureteroscopes [15-788]
238. Ureteroscopes, Flexible [18-188]
239. Ureteroscopes, Rigid [18-189]
240. Urethroscopes [14-289]
241. Urinary Collection Bags, Infant [16-782]
242. Ventilators, Intensive Care, Neonatal/Pediatric [14-361]
243. Ventilators, Intensive Care, Neonatal/Pediatric, High-Frequency [18-793]
244. Ventilators, Intensive Care, Neonatal/Pediatric, Negative Pressure [18-794]
245. Ventilators, Portable/Home Care [17-423]
246. Ventilators, Transport [18-098]
247. Warming/Cooling Units, Patient, Circulating-Fluid [12-074]
248. Warming/Cooling Units, Patient, Forced-Air [18-851]
249. Warming Units, Patient, Circulating-Fluid [17-648]
250. Warming Units, Patient, Forced-Air [17-950]
251. Warming Units, Patient, Radiant, Infant [17-956]
252. Warming Units, Patient, Radiant, Infant, Mobile [17-433]
253. Wheelchairs, Mechanical, Disabled Patient, Pediatric [18-409]

PART II: IMPLANTS

This list includes all implant types. Some come in pediatric sizes; some do not. Some implants are not recommended for children who have not reached a certain stage of development, for example, 80 percent skeletal maturity or adult brain size.

1. Allografts [17-165]
2. Annuloplasty Rings [16-039]
3. Aqueous/Vitreous Humor Replacement Media [16-844]
4. Batteries, Implantable Device [18-554]
5. Batteries, Implantable Device, Cardiac Pacemaker/Defibrillator [17-883]
6. Bolts, Bone [16-077]
7. Bone Matrix Implants, Artificial [17-751]
8. Bone Matrix Implants, Biological [17-756]
9. Brachytherapy Sources [17-518]
10. Caps, Bone [16-082]
11. Caps, Nerve [16-083]
12. Catheters, Cardiac, Hydrocephalic [16-086]
13. Cement, Orthopedic [12-830]
14. Clips, Aneurysm [10-905]
15. Clips, Fallopian Tube [14-174]
16. Clips, Ligating [16-052]
17. Clips, Vascular [16-028]
18. Clips, Vena Caval [10-915]
19. Conformers, Ophthalmic [16-065]
20. Corneas, Eye [17-108]
21. Defibrillator/Cardioverters [18-502]
22. Defibrillator/Cardioverters, Implantable [18-503]
23. Defibrillator/Cardioverter/Pacemakers, Implantable [18-504]
24. Defibrillator/Cardioverter/Pacemakers, Implantable, Resynchronization [20-376]
25. Defibrillator/Pacemakers, Implantable [17-989]
26. Defibrillators, Implantable [16-652]
27. Expanders, Skin [16-045]
28. Eyelid Weights, Implantable [18-074]
29. Fasteners, Helical [18-797]
30. Fasteners, Helical, Surgical Mesh [18-507]
31. Fasteners, T [18-796]
32. Fasteners, T, Percutaneous Gastrostomy [17-789]
33. Felts, Cardiovascular [16-030]
34. Filters, Vena Cava [11-718]

35. Gastroplasty Bands [17-649]
36. Glaucoma Filtration Implants [17-618]
37. Grafts, Bone [11-910]
38. Grafts, Bone, Synthetic [16-966]
39. Grafts, Dura, Biological [17-462]
40. Grafts, Skin, Artificial [18-254]
41. Grafts, Skin, Biological [18-253]
42. Hemodialysis Needle Sets, Protective [18-246]
43. Infusion Pumps, Implantable [16-143]
44. Intracorneal Rings [18-103]
45. Intrauterine Devices [12-156]
46. Leads, Implantable Defibrillator [16-653]
47. Leads, Implantable Defibrillator/Pacemaker [17-964]
48. Leads, Implantable Defibrillator/Pacemaker, Resynchronization [20-377]
49. Leads, Pacemaker, Implantable Endocardial [12-900]
50. Leads, Pacemaker, Implantable Myocardial [11-458]
51. Leads, Spinal Cord, Implantable [17-215]
52. Lenses, Intraocular, Anterior Chamber [16-068]
53. Lenses, Intraocular, Iridocapsular Fixation [16-069]
54. Lenses, Intraocular, Iris Fixation [16-070]
55. Lenses, Intraocular, Posterior Chamber [16-071]
56. Mesh, Metallic [16-048]
57. Mesh, Polyglycolic Acid [17-247]
58. Mesh, Polymeric [12-510]
59. Mesh Bags, Pacemaker [16-038]
60. Microspheres [20-399]
61. Microspheres, Embolization [20-400]
62. Microspheres, Embolization, Brachytherapy [20-372]
63. Microspheres, Embolization, Drug Delivery [20-403]
64. Microspheres, Embolization, Hyperthermia [20-402]
65. Nails, Bone [16-078]
66. Occluders, Cardiac Septum [20-414]
67. Occluders, Umbilical Cord [20-416]
68. Occluders, Vascular [17-731]
69. Occluders, Vascular, Intravascular Embolization [15-034]
70. Occluders, Vascular, Intravascular Embolization, Particulate [20-412]
71. Occluders, Vascular, Presacral Bleeding [20-413]
72. Ophthalmic Foil [16-066]
73. Orthopedic Internal Fixation Systems, Fracture [12-833]
74. Orthopedic Internal Fixation Systems, Spinal [15-766]
75. Pacemaker Lead Adapters, Implantable [17-635]

76. Pacemakers, Breath [18-496]
77. Pacemakers, Breath, Diaphragmatic/Phrenic Nerve [16-060]
78. Pacemakers, Cardiac, Implantable [12-913]
79. Pacemakers, Cardiac, Implantable, Resynchronization [20-375]
80. Patches, Myocardial [13-165]
81. Pins, Bone [16-085]
82. Pins, Dental Retention [16-700]
83. Plates, Bone [13-050]
84. Plates, Cranioplasty [13-052]
85. Plates, Dental [20-331]
86. Plates, Dental, Implantable Staple [16-203]
87. Pledgets [13-055]
88. Ports, Injection/Infusion [16-854]
89. Ports, Injection/Infusion, Central Venous [18-765]
90. Ports, Injection/Infusion, Peripheral Vessel [18-766]
91. Power Supplies, Regulated, Staple Reshaping [20-332]
92. Prostheses, Bile Duct [13-135]
93. Prostheses, Bladder Support [13-136]
94. Prostheses, Blood Vessel, Artificial [13-177]
95. Prostheses, Blood Vessel, Biological [11-913]
96. Prostheses, Bone, Freeze-Dried [16-862]
97. Prostheses, Cardiac Valve, Artificial [15-869]
98. Prostheses, Cardiac Valve, Biological [15-870]
99. Prostheses, Cardiac Ventricle, Percutaneously Powered [20-491]
100. Prostheses, Cardiac Ventricle, Transcutaneously Powered [20-492]
101. Prostheses, Carpal [16-089]
102. Prostheses, Cerclage, Bone [16-140]
103. Prostheses, Cerclage, Cervix [13-139]
104. Prostheses, Chin [13-140]
105. Prostheses, Dental, Implantable [16-744]
106. Prostheses, Esophageal [13-145]
107. Prostheses, Eustachian Tube [15-324]
108. Prostheses, Evisceration [16-067]
109. Prostheses, Fallopian Tube [13-148]
110. Prostheses, Finger/Thumb [16-094]
111. Prostheses, Foot Arch [16-135]
112. Prostheses, Gastroesophageal Antireflux [16-165]
113. Prostheses, Heart [13-152]
114. Prostheses, Heart, Percutaneously Powered [16-977]
115. Prostheses, Heart, Transcutaneously Powered [20-398]
116. Prostheses, Joint, Ankle [16-132]
117. Prostheses, Joint, Ankle, Tibial Component [16-088]
118. Prostheses, Joint, Elbow [16-105]

119. Prostheses, Joint, Elbow, Humeral Component [16-091]
120. Prostheses, Joint, Glenoid Bone [18-023]
121. Prostheses, Joint, Hip, Acetabular Component [16-084]
122. Prostheses, Joint, Hip, Femoral Component [16-095]
123. Prostheses, Joint, Hip, Total [16-150]
124. Prostheses, Joint, Knee, Femoral Component [16-097]
125. Prostheses, Joint, Knee, Patellar Component [16-121]
126. Prostheses, Joint, Knee, Tibial Component [16-098]
127. Prostheses, Joint, Knee, Total [16-096]
128. Prostheses, Joint, Mandible [16-962]
129. Prostheses, Joint, Shoulder [16-099]
130. Prostheses, Joint, Temporomandibular, Disk [18-024]
131. Prostheses, Joint, Temporomandibular, Total [17-479]
132. Prostheses, Joint, Toe [16-134]
133. Prostheses, Joint, Wrist [13-168]
134. Prostheses, Larynx [13-159]
135. Prostheses, Ligament [16-242]
136. Prostheses, Mammary, Internal, Gel-Filled [17-855]
137. Prostheses, Mammary, Internal, Inflatable [17-854]
138. Prostheses, Mandibular [16-047]
139. Prostheses, Maxillofacial [13-162]
140. Prostheses, Meningeal [15-961]
141. Prostheses, Muscle [13-164]
142. Prostheses, Nasal, Dorsal [16-036]
143. Prostheses, Nerve Sheath [16-057]
144. Prostheses, Nipple [16-130]
145. Prostheses, Orbital Rim [16-113]
146. Prostheses, Ossicular, Incus/Stapes [16-107]
147. Prostheses, Ossicular, Total [16-108]
148. Prostheses, Penile, Inflatable [17-997]
149. Prostheses, Penile, Rod [17-998]
150. Prostheses, Pericardial [17-800]
151. Prostheses, Radial Head [17-101]
152. Prostheses, Radial/Ulna Head [16-259]
153. Prostheses, Rhinoplasty [16-115]
154. Prostheses, Tendon [13-171]
155. Prostheses, Testicle [13-172]
156. Prostheses, Tracheal [15-050]
157. Prostheses, Tracheobronchial [13-174]
158. Prostheses, Urethral [13-175]
159. Prostheses, Urethral Sphincter [13-176]
160. Prostheses, Zygomatic [16-116]
161. Reconstruction Blocks, Plastic Surgery [16-043]

162. Reconstruction Sheeting, Plastic Surgery [16-118]
163. Resinous Compounds, Cranial [16-131]
164. Restrictors, Orthopedic Cement [16-126]
165. Root Canal Posts [16-202]
166. Screws, Bone [16-101]
167. Screws, Cranioplasty Plate [16-056]
168. Sheets, Cranioplasty [16-058]
169. Shunts, Arteriovenous [13-586]
170. Shunts, Endolymphatic [16-033]
171. Shunts, Hydrocephalic [16-244]
172. Shunts, Peritoneovenous [13-589]
173. Shunts, Pleuroperitoneal [17-218]
174. Sleeves, Eye Muscle [16-074]
175. Spacers, Tendon [16-102]
176. Staples, Bone, Compression, Heat Reshaping [20-327]
177. Staples, Gastrointestinal/Internal Organ [20-328]
178. Staples, Vascular [20-329]
179. Stent/Grafts, Vascular [18-585]
180. Stent/Grafts, Vascular, Aortic [20-453]
181. Stent/Grafts, Vascular, Aortoiliac [20-454]
182. Stent/Grafts, Vascular, Coronary [20-452]
183. Stent/Grafts, Vascular, Peripheral [20-455]
184. Stents, Biliary [17-672]
185. Stents, Biliary, Metallic [20-419]
186. Stents, Biliary, Metallic, Balloon-Expandable [20-420]
187. Stents, Biliary, Metallic, Self-Expanding [20-421]
188. Stents, Biliary, Polymeric [20-418]
189. Stents, Bronchial [17-957]
190. Stents, Bronchial, Metallic [20-432]
191. Stents, Bronchial, Metallic, Balloon-Expandable [20-433]
192. Stents, Bronchial, Metallic, Self-Expanding [20-434]
193. Stents, Bronchial, Polymeric [20-431]
194. Stents, Colonic [20-449]
195. Stents, Esophageal [17-928]
196. Stents, Esophageal, Metallic [20-443]
197. Stents, Esophageal, Metallic, Self-Expanding [20-444]
198. Stents, Esophageal, Polymeric [20-442]
199. Stents, Laryngeal [20-441]
200. Stents, Pancreatic [17-717]
201. Stents, Pancreatic, Metallic [20-446]
202. Stents, Pancreatic, Metallic, Balloon-Expandable [20-448]
203. Stents, Pancreatic, Metallic, Self-Expanding [20-447]
204. Stents, Pancreatic, Polymeric [20-445]

205. Stents, Tracheal [17-448]
206. Stents, Tracheal, Metallic [20-437]
207. Stents, Tracheal, Metallic, Balloon-Expandable [20-438]
208. Stents, Tracheal, Metallic, Self-Expanding [20-439]
209. Stents, Tracheal, Polymeric [20-435]
210. Stents, Tracheal, Polymeric, T-Shaped [20-436]
211. Stents, Tracheobronchial [20-440]
212. Stents, Ureteral [16-040]
213. Stents, Urethral [17-889]
214. Stents, Vaginal [16-041]
215. Stents, Vascular [17-461]
216. Stents, Vascular, Carotid [20-426]
217. Stents, Vascular, Carotid, Self-Expanding [20-427]
218. Stents, Vascular, Coronary [18-237]
219. Stents, Vascular, Coronary, Balloon-Expandable [20-422]
220. Stents, Vascular, Coronary, Balloon-Expandable, Bioactive-Coated [20-384]
221. Stents, Vascular, Coronary, Balloon-Expandable, Drug-Eluting [20-383]
222. Stents, Vascular, Coronary, Self-Expanding [20-425]
223. Stents, Vascular, Peripheral [18-238]
224. Stents, Vascular, Peripheral, Balloon-Expandable [20-429]
225. Stents, Vascular, Peripheral, Self-Expanding [20-430]
226. Stents, Vascular, Peripheral, Self-Expanding, Iliac [18-239]
227. Stents, Vascular, Renal Artery [20-428]
228. Stimulators, Electrical, Auditory [18-483]
229. Stimulators, Electrical, Auditory, Cochlear [16-035]
230. Stimulators, Electrical, Bone Growth, Implantable [18-482]
231. Stimulators, Electrical, Brain, Analgesic [16-061]
232. Stimulators, Electrical, Brain, Antiseizure [17-913]
233. Stimulators, Electrical, Brain, Psychiatric Therapy [17-758]
234. Stimulators, Electrical, Brain, Tremor [18-468]
235. Stimulators, Electrical, Cardiac, Myoplasty [18-145]
236. Stimulators, Electrical, Carotid Sinus Nerve, Blood Pressure [13-768]
237. Stimulators, Electrical, Neuromuscular, Bladder/Bowel Evacuation [16-029]
238. Stimulators, Electrical, Neuromuscular, Gait, Implantable [18-478]
239. Stimulators, Electrical, Neuromuscular, Grasp [18-475]
240. Stimulators, Electrical, Neuromuscular, Incontinence, Implantable [17-784]
241. Stimulators, Electrical, Peripheral Nerve, Analgesic, Implantable [18-473]

242. Stimulators, Electrical, Spinal Cord, Analgesic [17-241]
243. Stimulators, Electrical, Vagus Nerve, Antiseizure [18-474]
244. Symblepharon Rings [16-073]
245. Tacks, Sacculotomy [16-080]
246. Tissue Reconstructive Materials, Fluid [17-876]
247. Tissue Reconstructive Materials, Solid [16-153]
248. Trial Prostheses, Joint, Hip, Acetabular Component [18-164]
249. Trial Prostheses, Joint, Hip, Femoral Component [18-165]
250. Tubes, Laryngectomy [12-292]
251. Tubes, Myringotomy [15-323]
252. Tubes, Tracheostomy [14-096]
253. Valves, Ear [14-328]
254. Valves, Eye [14-329]
255. Valves, Hydrocephalic [17-090]
256. Washers, Bone Screw [17-856]
257. Wires, Bone [16-104]

C

The Dynamics of Pediatric Device Innovation: Putting Evidence in Context

*Annetine C. Gelijns, Ph.D., Brigid Killelea, M.D., Michael Vitale, M.D., Vipul Mankad, Alan Moskowitz, M.D.**

INTRODUCTION

There are several compelling reasons to study the dynamics of device innovation and evaluation in pediatrics. First, this innovation process has been much less studied than its counterparts in pharmaceuticals or biotechnology, although devices address many of the same critical clinical needs as drugs. Yet, there are important differences between pharmaceutical and device innovation, such as the structure of the industry, the role and importance of academic medical centers, and the degree of ongoing, incremental innovation that is the hallmark of the device evolution process. In device innovation, not only does the device undergo incremental change, but there is also substantial change in the ways in which device recipients are managed, including implantation/insertion procedures, their hospital care, and outpatient management. Such changes occur both in the pre- and postmarket settings, which raise challenges for the evaluative enterprise.

A second reason to study the device innovation process is that there are important unmet needs for novel or improved pediatric devices. These needs differ in many ways from those of the adult population. For example, children need smaller devices; a growing number of congenital heart defects require heart valves and occlusion devices sized appropri-

*International Center for Health Outcomes and Innovation Research, Columbia University, New York (Drs. Gelijns, Killelea, Vitale, and Moskowitz) and Department of Pediatrics, University of Kentucky College of Medicine, Lexington (Dr. Mankad).

ately for infants (AAP et al., 2004). Physiologic differences also play a role; children have higher heart rates, and this may reflect itself in more rapid calcification of prosthetic valves, which affect the materials used in these products. Children also have different inspiratory flow rates and different abilities to coordinate manual tasks. For example, devices for inhaled administration of drugs need to accommodate timing the activation of an inhaler with the child's intake of air. Lifestyle differences also play an important role for designing devices for children. For example, cochlear implants have been known to deprogram in response to contact with plastic playground slides (see Appendix F). Since children's life spans are longer, devices that are left in place for long periods of time, such as cranio-facial prostheses, may show increased rates of polymer plate absorption. On the other hand, devices may need to be replaced more frequently as they wear out; growing children may require larger devices as they age (AAP et al., 2004).

A third reason to study this topic is that the evaluation of pediatric devices offers unique challenges. Similar to devices for use in adults, devices for use with children are subject to U.S. Food and Drug Administration (FDA) regulatory requirements. When FDA clearance or approval of a device requires clinical data, trials may provide important information on safety and efficacy. However, even the most rigorous trials have inherent limitations in terms of measuring long-term outcomes (especially in younger patients) and the ultimate generalizability of their findings. Given the small patient populations for many pediatric devices, premarket studies are often single-arm studies or registries as part of a Humanitarian Device Exemption (HDE) approval process, which may lead to increased uncertainty in terms of the knowledge gained. The incremental nature of the device innovation process and the inherent limitations of premarket studies argue for ongoing monitoring and evaluation of the outcomes in widespread clinical use. Ongoing evaluation is costly, however, and of particular concern in the realm of pediatric medical devices, where the markets are small and the economic incentives to innovate weak.

This paper explores these issues in pediatric devices, and, among the broad spectrum of devices that range from tongue blades to imaging machines, focuses specifically on the more technologically sophisticated end of the spectrum. It first reviews the main players in device innovation and the policy environment in which they operate. It then analyzes the dynamics of pediatric device innovation and evaluation, and the challenges inherent in designing and conducting premarket and postmarket clinical trials. The paper concludes with some observations about possible analytical, institutional, and economic solutions to improving the knowledge base about devices, while at the same time, fostering much needed innovation in this area.

THE PLAYERS IN MEDICAL DEVICE INNOVATION

In today's knowledge-based economy, medical device innovations arise within a complex network of public and private sector institutions, including universities, national laboratories, and industrial firms (Gelijns and Thier, 2002). These institutions operate in an environment increasingly affected by governmental rules and incentives, which, in turn, shape the interactions among these institutions.

The Medical Device Industry and Its Markets

The Second World War brought about a fundamental transformation of the medical device industry. Wartime research stimulated many broad advances in science and engineering, such as microwaves, radar, ultrasound, and new materials. In the late 1940s, the transistor was invented—ushering in the era of low-power electronics and microelectronics (Gelijns and Rosenberg, 1998). These would prove to be of great benefit to the development of medical devices and had much to do with the post-war growth of the industry. Over the past few decades, the medical device industry has expanded dramatically. By 1992 there were roughly 1,700 different types (not including model variations) of medical devices, developed by approximately 10,000 to 11,000 device firms, either domestic or foreign, operating in the United States (FDA, 1992). By 2001, the number of firms had increased to about 16,000. These firms introduce over 7,500 new and modified products into health care annually; the vast majority of these, however, fall into low-tech medical equipment categories (Feigal, 2003).

The medical device industry is a highly fragmented industry consisting of start-ups and giant corporations. In 2001, 67 percent of publicly traded medical device firms had fewer than 20 employees, and only 6 percent had more than 500 (U.S. Department of Commerce as referenced in AdvaMed, 2004). The role played by firms of different size on the medical device industry is not entirely clear, although it is often asserted that small firms play a disproportionately large role in making the initial innovations (Lewin Group, 2000). These companies are research focused, specializing in the "front end" of R&D. Perhaps not surprisingly, a study by the Wilkerson Group concluded that "nearly all significant new and innovative products and procedures were pioneered by start-up companies." Indeed, in their survey they cite 29 major advances in therapy, all of which are attributed to start-ups (Wilkerson Group, 1995).

By comparison, large firms are crucial in determining the eventual commercial success of new devices (NAE, 2003). Their organizational assets include the following. First, they have an ability to navigate the com-

plex regulatory requirements surrounding the introduction of new products into health care. Firms build skills in managing clinical trials and serving the needs of regulatory agencies over time through multiple product filings. Second, large companies often have considerable skills in manufacturing and marketing. First-mover advantages are not always of primary importance to eventual success in the marketplace when new technologies possess certain significant commonalities with earlier ones (e.g., magnetic resonance imaging [MRI] with computer tomography [CT] scanning). Although the large multinational firms often entered the MRI field late, they quickly traversed the ground already covered by pioneering small firms, and asserted their skills in marketing and servicing, as well as their already established reputations in the CT field, to assume dominant positions in MRI (Gelijns and Rosenberg, 1998; Trajtenberg, 1990). Third, these companies understand the purchasing patterns of multiple stakeholders in a complex hospital environment. Hospitals prefer to contract with a limited number of suppliers, and so device companies need to offer a full product line of compatible products to meet buyers' needs. As such, large companies have a clear advantage over small companies who may manufacture only one device.

The global medical devices market has more than doubled since 1991, when the worldwide market was about $70 billion (The Lewin Group), to $169 billion in 2000 (AdvaMed, 2004). The United States market accounted for 43 percent of the 2001 total.[1] Although it has been declining in recent years, the United States has long run a positive balance of trade in medical device categories (in 2002 this surplus averaged about $3.3 billion; U.S. International Trade Commission). The market can be subdivided into various broad segments (Wilkerson, 1995). These include specialty devices and implantable products, medical and surgical supplies, imaging systems and other equipment (such as patient telemetry monitoring), *in vitro* diagnostics, and, the more recently expanding, health information systems segment. According to current estimates, the demand for medical devices is expected to grow, with the domestic demand for implantable devices expected to exceed $24 billion by 2007, up from $8.7 billion in 1997 (Freedonia Group, 2003). But within these apparently large markets, companies capture relatively few sales from any single product. Even "blockbuster" products in this industry rarely exceed $100 million. The medical device industry is very dynamic, characterized by short product life cycles.

[1]Because the U.S. medical device market is a vital part of the global device market, all major firms throughout the world participate in the U.S. market: most leading foreign firms have U.S. sales subsidiaries, and many also have extensive research and manufacturing activities in the U.S. In the same way that many foreign firms participate in the U.S. medical device market, most major U.S. firms sell goods throughout the world.

Patents provide less protection than in pharmaceuticals, and competitors are able to invent around existing patents. Consequently, research activity is intense, with 11.5 percent of sales invested in R&D for all device firms (Figure C.1), and probably up to 18 percent of sales reinvested in R&D by the more innovative firms, a figure comparable with that of pharmaceutical companies (AdvaMed, 2004).

There is a paucity of data on the universe of medical device firms manufacturing pediatric devices and the size of these markets. Children represent about 30 percent of the population and less than 12 percent of personal health care spending (NACHRI, 2001). Looking at the total number of hospitalizations in 2000, there were 36,417,565 for adults and 3,501,901 for children other than normal newborns—about 10 percent of the adult population (NACHRI, 2001). Of course, the spectrum of hospitalizations in children differs from adults, and may not involve therapeutic devices in the same proportion as in adult hospitalizations. Indeed, pediatric medical device markets are typically very small. For example, the market for left ventricular assist devices (LVADs) for children over 6 years of age is expected to be around 150–200 devices annually.[2]

Universities and Their Academic Health Centers

The private sector relies heavily upon an infrastructure of institutions and research activities within the academic realm (Gelijns and Rosenberg, 1999). Research universities are key players in the medical device innovation system, with advances in physics, materials sciences, optics, analytical methods, and computer science often being generated in departments of physics, chemistry, computer sciences, or engineering schools. Moreover, in recent decades bioengineering research has emerged as a separate discipline, with 70 universities and colleges offering bioengineering degrees in 1998 (NAE, 2003).

Within universities, academic medical centers (AMCs) play a particularly important role in the development of medical devices. Around the country, academic medical centers may have a slightly different organizational structure, but they are generally comprised of a medical school, its teaching hospital, a potential network of affiliated hospitals, and a nursing school. An academic medical center may also involve a school of dentistry, a school for allied health professionals, and a school of public health. These complex, multifunctional organizations have a three-pronged mission: (1) they train clinicians and biomedical researchers and, thereby, shape the distribution of medical skills and specialties; (2) they provide advanced

[2]From personal communication with Betty Russell, Chief Operating Officer, Micromed, Inc.

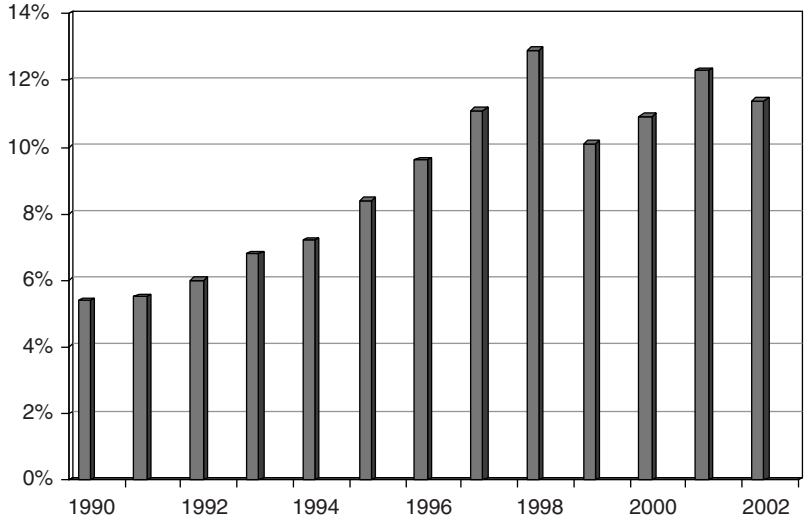


FIGURE C.1 Medical device R&D spending as a percent of sales.
SOURCE: S&Ps Compustat. Data from publicly traded companies. From AdvaMed (2004).

specialty and tertiary care, and as such are early adopters of the "latest" in technology. With a large patient population, a wide referral base, and a research-oriented attending staff, academic medical centers also attract patients with rare diseases, making them an ideal place to develop and test new devices and orphan drugs; and (3) they conduct a whole range of biomedical research activities, ranging from laboratory-based fundamental research to population-based clinical studies. Such evaluative studies may yield clinical data that may provide support for FDA approval, coverage by payers, and postmarket surveillance of pediatric devices. There are around 250 children's hospitals in the United States, which account for a substantial percentage of all National Institutes of Health (NIH)-funded pediatric research (NACHRI, 2001). Almost all of these centers participate in clinical trials and health-related research, and about one-third of these centers have child health research centers where interdisciplinary research is conducted (NACHRI, 2001).

In the United States, AMCs, and basic biomedical research in particular, have been major beneficiaries of post-war science policy. The research budget of NIH was nearing $30 billion in 2003, and nearly 80 percent of its extramural monies are spent in AMCs, providing strong support for their research enterprise.[3] At the same time that biomedical research spending

[3]Award data available at: http://grants.nih.gov/grants/award/award.htm. Accessed 3/9/2005.

increased significantly in the post-war years, health insurance coverage of the American people expanded, which has paid AMCs handsomely for their patient care and educational activities. There is a close interdependence, as we will explore, between AMCs and device firms throughout the different stages of the innovation process. These close university–industry interactions were also fostered by public policy, such as the creation of the Bayh Dole Act in 1980 (P.L. 96–517), which provided incentives to patent and license the findings of publicly funded research.

THE POLICY ENVIRONMENT

The government plays a multifaceted role in the device innovation process. It supports medical R&D, regulates the marketing approval of new devices and provides postmarket oversight. It also pays for clinical interventions through Medicare, Medicaid, and numerous other benefit programs.

Federal Support for Research and Development

Federal support for R&D in medical devices flows through multiple institutional and disciplinary channels. Although the majority of medical device-related R&D funds are spent in AMCs, federal agencies also fund basic and applied research in academic science departments and engineering schools, federal laboratories, and industry proper.

Compared to other countries that are members of the Organisation for Economic Co-operation and Development, the United States spends the largest amount of its overall research budget in the life sciences (over 50 percent). The largest single medical research funding agency is the NIH, and most of its nearly $30 billion budget is spent on extramural research in AMCs, particularly in non-human bench research. In 2003, NIH funding of children's hospitals and pediatric departments was approximately $961 million.

Only a small portion of the NIH budget is used to create opportunities for the development of devices. In 2000, NIH created the National Institute for Biomedical Imaging and Bioengineering (NIBIB) "to improve health by promoting fundamental discoveries, design and development, and translation and assessment of technological capabilities" (NIBIB, 2005). NIBIB's fiscal year 2004 budget was over $288 million (DHHS, 2004).

The pre-existing NIH institutes also have device R&D programs, including programs specifically for children. A case in point is the National Heart, Lung, and Blood Institute (NHLBI). The NHLBI created the artificial heart program to support the development of a family of devices to assist the failing heart and to rehabilitate patients with heart failure. In 2003, the NHLBI requested proposals to develop novel circulatory assist

devices for infants and children. This followed the recommendations of a NHLBI task force to invest more funds in the area of pediatric cardiovascular disease (NHLBI, 2002). They also recommended establishing a clinical trials network to implement multi-center, randomized studies for assessing new and emerging therapies. Part of the network's charge is to create registries for the longitudinal follow-up of children, which would address late risk of specific heart defects and treatments.

In 2000, Congress passed the Children's Health Act of 2000 (P.L. 106–310), which created the Pediatric Research Initiative to be housed within the Office of the Director of NIH. The objectives were to increase support for pediatric research, strengthen collaborative efforts among institutes and centers, and speed development of pediatric clinical drug trials. No new funds were appropriated by Congress, but the Office of the Director allocated $5 million for the initiative from its discretionary account for one year only (FY2002). (According to an analysis by Gitterman and colleagues, between 1998 and 2005 when the NIH budget doubled, pediatric spending by NIH increased by an average annual rate of 12.8 percent compared to an overall NIH average growth rate of 14.7 percent. The proportion of the total NIH budget devoted to the pediatric portfolio declined from 12.3 percent to 11.3 percent.)

Regulation

The FDA is charged with the formidable task of approving medical products as they enter the market and regulating devices in the postmarket period. Broadly speaking, the Medical Device Amendments of 1976 expanded the FDA's responsibility in this field, with the intention to ensure that new devices brought to market were both safe and effective. It divided medical devices into three classes, with high-risk devices (i.e., devices that are life-supporting or sustaining, that are of substantial importance in preventing impairment of health, or that have a potential for causing risk of injury or illness) being grouped in Class III. These Class III devices, about 10 percent of all devices, must demonstrate safety and efficacy in clinical trials before the FDA grants marketing approval.[4]

[4]Class I devices include instruments that do not support or sustain human life (e.g., stethoscopes), and do not present an unreasonable risk of illness or injury. Class II devices include x-ray machines and other devices that pose some risk. Over 90 percent of devices fall into Class I and Class II devices. Finally, Class III devices pose the highest level of risk; examples include left ventricular assist devices (LVADs), DNA probes, or laser angioplasty devices. Any device introduced since 1976 is automatically placed in Class III unless the sponsor successfully petitions the FDA to reclassify it as "substantially equivalent" to a device that was on the market before the amendments took effect. Demonstration of this equivalence through a 510(k) submission, is provided by descriptive, performance, and sometimes clinical data.

FDA regulation of medical devices has been undergoing significant change. The introduction of the Safe Medical Devices Act of 1990, for example, established new requirements for premarket, as well as postmarket studies. As far as premarket studies are concerned, device manufacturers are now required to conduct more rigorous studies with appropriate, and where possible, randomized controls. In the area of postmarket surveillance, a number of separate mechanisms exist for collecting data. Device manufacturers as well as health care providers must submit adverse event reports to FDA if a device may have caused or contributed to a death or serious injury. In the case of high-risk devices, companies must keep track of patients, and, in certain cases, the FDA requires post-approval clinical studies to detect possible risks associated with device use, as well as to provide information on effectiveness. The changes incorporated in the Safe Medical Devices Act should encourage higher quality device evaluations and provide more useful information about safety and efficacy. At the same time, some of these changes also have important consequences for the timely introduction of new medical devices to market, and for the degree of financial risk and costs associated with the innovation process.[5]

For some Class III devices, especially those targeted to a narrow market such as is often the case in pediatrics, gathering sufficient evidence for premarket approval may be a lengthy and/or risky process because of the small number of affected patients. Therefore, for diseases that affect fewer than 4,000 people per year in the United States, the FDA may grant a Humanitarian Device Exemption. An approved HDE allows for marketing of these devices without the rigorous clinical and non-clinical PMA effectiveness requirements, provided that there is no alternative device, the device would otherwise not be available, and the manufacturer shows that reasonable safety and probable benefit to the patient outweighs the risk of injury or illness. An approved HDE authorizes limited marketing of a Humanitarian Use Device (HUD) (FDA, 2001). There have been 130 HDE applications since the inception of the HDE program, but only 30 have been approved. Manufacturers are not allowed to make profits on these devices; they may

To support marketing approval decision for a Class II device, or in some instances a 510(k) submission (about 10 percent of submissions), a sponsor must conduct clinical studies. If a device poses a significant risk (Class III), the sponsor must submit a request for an Investigational Device Exemption (IDE) to the FDA. Following clinical studies, a device may be approved for marketing through a so-called premarket approval decision (PMA).

[5]In the early 1990s, FDA review times for IDEs, PMAs, and 510(k) submissions were long, and the agency had a considerable backlog. The FDA subsequently reorganized its device branch, and the FDA Modernization Act (P.L. 105–115, also known as FDAMA) was introduced in 1997. FDAMA is a wide-ranging piece of legislation, which attempts to move resources within the agency from relatively low-risk to relatively high-risk areas, specify the requirements for clinical device trials, and so on. As a result of changes within the agency, the backlog has diminished substantially and review time improved considerably.

only recover the costs of production. Currently, there are six active HDEs for pediatrics, including the LVAD, a heart valve, bladder stimulator, and fetal bladder stent, gastric stimulator, and cultured skin. Table C.1 list some representative pediatric devices approved for marketing or as part of an HDE.

TABLE C.1 Some Recently Approved Devices Tested for Use in Children[a]

Device	Ages	Category
† β Vertical Expandable Prosthetic Titanium Rib (VEPTR)	Not for use in children younger than 6 months of age or after skeletal maturity (about age 14 for girls, 16 for boys)	Prostheses
† β DeBakey VAD® Child	For children aged 5 to 16 years	Heart Devices, Ventricular Assist Device
† β Contegra® Pulmonary Valved Conduit, Models 200 and 200S	For children under age 18	Heart Devices, Heart Valves
Medtronic Activa® Dystonia Therapy	For children aged 7 and older	Stimulator
Mentor Saline-Filled Testicular Prosthesis	Tested in adults and children 0.5 to 17 years of age	Prostheses
†AMPLATZER® PFO Occluder	Tested in adults and children aged 11 and older	Heart Devices
†AMPLATZER® Septal Occluder	Tested in adults and children 7 months of age and older	Heart Devices
NNMT Medical, Inc. CardioSEAL Septal Occlusion System with QwikLoad	Tested in children 4 months of age and older	Heart Devices
β Deflux Injectable Gel	For children 1 year of age and older	Urology, Vesicoureteral Reflux
GlucoWatch G2 Biographer	For children aged 7 to 17	Glucose Monitoring Device
Nucleus 24 Auditory Brainstem Implant System	For children 12 years of age and older	Auditory Implant, Brain Stimulator, Hearing Devices, Stimulator

NOTE: † Denotes device approved under the Humanitarian Device Exemption (HDE) Program. β Denotes device approved for use in pediatrics only.
[a]Devices approved since October 2000.

Reimbursement

Decisions about medical coverage and reimbursement for use of pediatric devices are made primarily by individual state Medicaid programs and by commercial health insurance companies. These decisions influence not only the quality of health care for children, but also the innovation process, marketing, and availability of devices for children. Absence of or insufficient reimbursement for a pediatric procedure or the costs of devices used during the procedure is often a significant barrier in development of a new pediatric device.

Within the Medicaid program, each state may develop its own benefit package (covering services that are deemed "reasonable and necessary") and set reimbursement rates within the broad framework of the 1965 Social Security Legislation and federal regulations. In doing so, some states use coverage decisions made by the Medicare program, while others have their Medical Directors make state-specific policies for coverage or use guidelines developed by commercial insurance companies in their regions. Until recently, few commercial payers (with some notable exceptions such as the Blue Cross and Blue Shield process) provided clear descriptions in their contracts of how coverage decisions were made, and there was no systematic process for gathering input from clinicians and consumers. In recent years, however, commercial payers are increasingly basing their coverage decisions on both clinical and economic evidence.

Following a coverage decision, billing codes are a necessary, critical pathway for reimbursement of services and procedures and the use of pediatric or other devices. The coding system, which was primarily designed for general use, often doesn't contain specific codes for pediatric devices, which may have different development and production costs than adult devices. This increases the risk of inadequate reimbursement for pediatric devices, which is a disincentive for innovation. Until recently, the coding revision and coverage decision process did not have input from Medicaid programs. The newly created system of public consultations to inform this process will also need to include pediatric providers, advocates for children with device needs, and device manufacturers to ensure that information that could affect pricing is taken into consideration.

Finally, if a code exists or is created for devices used with children, decisions by payers to set a reimbursement level vary and are subject to political pressures and negotiations. A recent Centers for Medicare and Medicaid Services (CMS) decision expanded the coverage of an implantable cardioverter–defibrillator (ICD) coupled with a requirement for development of additional evidence through large-scale, prospective, observational studies or registries (McClellan, 2005). Further characterization of the subgroups for which the device would be beneficial and of the real-world

clinical outcomes will add further information to allow the CMS to use public funds more effectively. A challenging task would be to link reimbursement decisions to postmarket surveillance of pediatric devices since it will require coordination of multiple state-operated Medicaid programs and commercial payers.

THE DYNAMICS OF DEVICE INNOVATION

The device innovation cycle can be seen to consist of various, partly overlapping, stages. These stages include research in the physical sciences and engineering, human physiology and pathophysiology; the development of novel product ideas, device prototypes, and manufacturing methods; the evaluation of devices in animals and humans; the modification of existing products; and the discovery of new indications for use. Generally, the development of a new device prototype is driven by the conjoining of new technological capabilities with the perception of unmet clinical needs.

Because the markets for medical devices are often fragmented and relatively small, the medical device industry has historically not invested heavily in basic research. In fact, the medical device industry often has been heavily dependent on scientific and technological capabilities that have been developed in other sectors of the economy. Medical device innovation exploits research and new technological capabilities and components that have been developed by universities, the military, the electronics industry, and a range of firms manufacturing essential, specialized materials, such as high-quality glass for fiber optics or inert materials for prosthetic devices. In addition to these developing technological capabilities, new insights into human physiology and pathophysiology have become increasingly central to the development of new devices. Understanding the electrophysiology of the heart, for example, has been critical for designing a pacemaker or implantable defibrillator, as is circulatory physiology for designing artificial hearts and circulatory assist devices. Similarly, renal physiology has been crucial in elucidating the pharmacodynamics and pharmacokinetics of hemodialysis, which, in turn, has contributed to the development of improved dialysis machines. These insights often have been generated in academic medical centers.

Development of Device Prototypes

The development of a new device prototype can occur either in industry or in a clinical setting, most often an academic medical center. Clinicians and academic researchers not only identify the need for a new device or for improvements in existing devices, but they may also be the innovators and builders of the original prototype because of their role as sophisticated

users. The importance of academic faculty in the development of device prototypes has been documented for a whole range of devices, such as the automated clinical chemical analyzer, renal dialysis machines, intrauterine devices, catheters, laparoscopes, fiber-optic endoscopes, and MRI machines (von Hippel and Finkelstein, 1979; Shaw, 1987; Gelijns, 1991; Gelijns and Rosenberg, 1995, 1998).

In the pediatrics realm, the Vertical Expandable Prosthetic Titanium Rib (VEPTR) is a recent device created by a practicing orthopedic surgeon. Dr. Robert Campbell recognized the need to insert a rib spacer to avert respiratory failure and early death in children with thoracic insufficiency syndrome from spinal and chest wall deformities (FDA, 2004a; Sansom, 2004). The device, which is curved, is inserted between ribs and allows the lungs to expand to a larger thoracic volume. As the child grows at roughly 6-month intervals, the device can be expanded through a simple outpatient surgery. The titanium rib has been implanted in children as young as 6 months of age, and is ideally left in place until the respiratory system is close to maturity. This surgically implantable device, which has been used under an HDE status, gained FDA approval in 2004 after it was used in approximately 250 children.

If initially developed in academia, innovators often discover that they are unable to advance the project because critical, enabling technologies are missing or are too technologically specialized to develop within the laboratory or elsewhere in the university. It is at this point that a partnership is often formed between the academic researcher and an industrial firm, which has the applicable technological expertise and interest in the proposed application.

Most devices are evaluated in animals and undergo bench testing before they are used in clinical testing. The reliability of the pediatric LVAD, for example, is generally tested in mock loop systems, and pre-clinical testing of the device, depending on the age of the recipient, can be done in dwarf pigs or calves.

Premarket Clinical Evaluation

Following bench and animal testing, some Class II and all Class III devices enter the stage of human evaluation. The clinical data generated by such testing form the basis for obtaining FDA premarket and payer coverage approval, and thereby lead to widespread market access. A small percentage of devices (i.e., Class III devices and a small subset of 510(k) devices) require rigorous safety and efficacy evaluation. As a result, a modest but growing number of devices undergo randomized, controlled trials or other prospective comparative studies. In recent years, clinical trial spending on devices by industrial firms has been growing substantially.

Clinical Trials Organizational Infrastructure

One can divide up the clinical trials infrastructure into organizations that coordinate the activities of clinical trials and those that actually provide the patient care, that is, clinical sites that conduct clinical trials. Device manufacturers, academic medical centers, and contract research organizations (CROs) all are engaged in clinical trials coordination, and each offers different strengths to the process. Device manufacturers have the greatest familiarity with the engineering and scientific principles of the devices, but few firms are large enough to have the personnel to design, conduct, and analyze trials. Moreover, they have financial interest in the outcome of studies, which might influence the credibility of the results. Academic medical center faculty has also been involved in the design, conduct, and analysis of clinical trials. However, during the last decade, contract research organizations have captured part of this market (Moskowitz, 2003). CROs are private, for-profit organizations that are engaged in the management of clinical trials, including protocol design, patient recruitment, data collection, data management, monitoring, and analysis. CRO usage among the medical device industry is not common; only 13 percent of medical device firms employ CROs (whereas 90 percent of drug firms use CROs), and few CROs have extensive experience conducting implantable device trials (Centerwatch, 2005).

Academic medical centers, community-based hospitals, and practices can be venues to enroll and treat patients, and collect data on their outcomes. Academic medical centers have traditionally been involved with the testing of prototype devices and have served as the source of patients for more involved clinical trials. In particular, they are the venue of care for more complex patients, which is common among patients who need implantable devices and invasive procedures.

Clinical Trial Design and Its Challenges

There is a spectrum of research designs employed in testing pediatric devices, ranging from randomized comparative trials to single-arm studies with historical controls. The first stage of clinical testing is usually a single-arm, prospective study in a diseased population to assess the feasibility of use in humans. These studies are generally small in size, and they provide only preliminary evidence about short-term safety and efficacy. The major value of these studies is that they offer *prima facie* evidence for designing larger-scale, pivotal trials. Optimally, these pivotal trials would be randomized or otherwise appropriately controlled studies and would incorporate a spectrum of endpoints. Over the past 20 years, there has been a transition from intermediate, physiological endpoints to more clinically relevant pa-

tient outcomes, such as survival, functional capacity, and quality of life. The advantage of the trend toward more clinically relevant outcome measures is that clinical and economic decision making is enhanced; the drawback is that it generally takes longer periods of observation to achieve these measures of outcome.

In comparison to pharmaceutical trials, device trials must contend with unique ethical, logistical, and methodological challenges. A major constraint in designing pediatric trials can be found in patient recruitment. In general, pediatric diseases are low prevalence, affecting the ability of researchers to recruit a sufficient number of participants in a reasonable period of time. Given the small market potential for many pediatric devices, there is already little economic incentive to pursue the development of new pediatric devices. This is compounded by the increased development costs associated with having to conduct comparative trials with large sample sizes, which would require a greater number of clinical centers or a longer enrollment period to capture the needed trial population. When randomized or other prospectively controlled studies are not feasible within a reasonable time frame, the FDA allows single-arm studies that use objective performance criteria derived from prior studies. Alternatively, they may allow comparative studies with a greater chance of a random variation error or, in other words, accept a higher p-value to establish statistical significance.

Another challenge, in comparison to pharmaceutical trials, is choosing the right time to take a device into the pivotal trial stage. A pharmaceutical compound generally does not undergo substantial change as it progresses through the various phases of clinical trials, except that development may be discontinued if the profile is undesirable, and a modified compound may enter pre-clinical and phase I trials. Devices, however, undergo extensive modifications and refinements during the clinical evaluation stages. These modifications are not only in the device itself, but also in the clinical management of a patient with a device. A case in point is the REMATCH trial, which evaluated the efficacy and safety of a left ventricular assist device for long-term therapy of end-stage heart failure patients. During this trial, various changes were implemented, such as a modification of the driveline, the introduction of a locking screw ring to prevent detachment of the blood-transport conduits to and from the pump, and a clinical protocol to better prevent and manage driveline infections with antimicrobial agents and laminar flow operating rooms. Such modifications in the device or clinical management can be accommodated in the design of clinical trials. In the REMATCH trial, for example, there was no change in the predetermined sample size (Rose et al., 2001). If, however, the device design or clinical management change offers a substantial change in the measures of outcome, additional patients may need to be recruited to accommodate specific subgroup analyses.

Once the optimal time to begin a pivotal clinical trial is established, decisions concerning which venue and which clinicians to engage in testing a particular device can have a major effect on how the results of the trial will be interpreted and whether the device achieves broader usage. In contrast to pharmaceuticals, the efficacy of a surgically implanted device can be linked to the skill of the implanting surgeon. If there is substantial variation in skill among trial investigators, the results of the trial may be difficult to interpret. A positive average outcome for the experimental therapy may only be positive because of a few exceptionally well-skilled clinical sites, and a negative average outcome may only be negative because of a few, poorly skilled clinical sites. Clinical researchers must be on the guard for such outcomes. Trials typically offer a separate randomization scheme for each clinical site so that each site is balanced with respect to the number of experimental and control patients that they treat. Moreover, examining the effect of study site on the primary outcome is a routinely performed analytical step. One strategy to assure uniformity of skill is to engage in a pilot trial or run-in period, which will not be counted in the final analysis. Another is to limit participation to individuals that have a particular skill level. Conducting a trial in a highly specialized center with unique surgical expertise may result in a successful trial, but may not be generalizable to widespread usage or provide useful information on the economic value of using the device in less specialized centers.

Pediatric patients are considered a vulnerable population in the context of conducting clinical research. Research that presents more than a minimal risk without the chance of direct benefit to the child is unlikely to be approved by an Institutional Review Board (IRB). Those trials that are approved involve special considerations regarding the informed consent process. Only the parent or legal guardian has legal standing for signing a statement of informed consent for a minor (the age cut-off varies by state). However, older children, who have the capacity to understand the activities involved in trial participation, need to give their assent for the participation.

Blinding, an important technique for controlling observational bias when evaluating the safety and efficacy of a new clinical intervention, is an issue in invasive or implantable device trials. Obviously, it is impossible for the clinician that implants a device to be blinded. Patient blinding is usually not possible when the comparative therapy is not a device. Thus, randomization is more of a problem in device trials because of the lack of blinding. This is true in particular when there is a life-threatening illness. Here both patient (their family) and physician will have expectations that the device is their best hope and would be devastated to learn, up front, that they would not receive the preferred therapy. This could deter some patients and physicians from entering into a device trial, while others might enroll but seek treatment outside the protocol if they didn't receive the therapy they wanted.

This might lead to a loss-to-follow-up or out-of-protocol crossover, which could ruin a small-scale trial. The ethical dilemma here is heightened when there are no alternative therapies and assignment to a control arm means essentially no therapy (Moskowitz et al., 1997).

Measuring survival in trials that compare devices and medical therapies poses methodological challenges. When device therapy involves a high up-front operative risk, but subsequently a reduced mortality compared to the control group, the survival curves are likely to cross. Analyzing the differences between such curves depends on the analytical method chosen and the time frame of the analysis. Most analytical methods (e.g., log-rank, Wilcoxon test) average risk over the follow-up period. So, extending or reducing the follow-up time has the potential to reverse the ordering of relative efficacy because less or more weight, respectively, will be given to the mortality in the peri-operative period (Rose et al., 1999).

Measuring the effects of treatment on children's quality of life is a more complex task than for adults, largely because children are developing (Rosenbaum and Saigal, 1996). Any assessment of functional status must be performed in a developmental context. Key aspects of quality of life (such as physical, emotional, and social function) develop rapidly as the child ages, which means that a group of questionnaires must be developed that are specific for an age group. Similarly, age-adjusted normative values are needed to put the measured values in the context of the general population. For younger children at an earlier stage of intellectual development, investigators must rely on parents or caretakers to act as proxies for direct patient-based responses. Despite these challenges, there has been considerable progress in the field of quality of life assessment for children, with new survey instruments, both generic and disease-specific, being developed and validated in a range of pediatric conditions (Drotar, 1998; Eiser and Morse, 2001; Koot and Wallander, 2001).

Assessment of the economic value of devices is challenging in pediatric populations for many of the same reasons that it is difficult to assess clinical outcomes. The small patient populations that frequently result in single-arm studies or registries hamper not only the identification of treatment effects, but also leave the assessment of cost-effectiveness without a comparator. The short-term nature of many randomized trials makes it difficult to accurately assess the long-term economic impact of treating a particular patient population for the individual payer. Economic analyses typically use outcomes such as costs per life year saved or quality-adjusted life-year (QALY) saved, which require survival projections. In the case of children with long life expectancies, these projections are more difficult to make and, consequently, involve greater uncertainty. Moreover, the tendency to conduct pediatric device trials in highly specialized treatment centers makes it difficult to infer the economic value of the use of devices in less special-

ized centers. In recent years, there has been an increase in economic evaluations for pediatric populations. Ungar and Santos (2003) created a pediatric economic database and documented a 7-fold increase in publications between 1980 to 1984 and 1995 to 1999. Currently, the database contains over 1,000 citations of full economic evaluations from January 1980 to the end of December 2003. However, searching the database for device-related economic evaluations, we found only 30 citations analyzing 11 different device categories (e.g., cochlear implants, amplatzer catherization techniques for occlusion of atrial septal defects, and laparoscopic spelenectomy). Most of these evaluations were conducted in the last 5 years, indicating an emerging trend.

In short, rigorous trials can provide important evidence about the efficacy, safety and—more recently—the economic impact of new pediatric devices. Regulatory decisions then have to combine this empirical evidence with qualitative judgments about the acceptability of the trade offs between benefits and risks associated with new technologies, and payers have to combine the empirical evidence with qualitative judgments about the acceptability of the trade-offs between benefits and costs. Such trade-offs depend upon the disease context and available alternatives, the preferences for the outcomes at stake, and the amount of uncertainty in achieving them. Given that premarket trials are based on a sampling process, there will always be uncertainties. Attempting to eradicate uncertainty is impossible, and attempts to bring the level of uncertainty down to minute levels would be costly in terms of the time and expense of the premarket development process, as well as the indirect expense of holding off a promising therapy from patients. Diminishing these uncertainties will require widespread clinical use and analyzing the outcomes in the postmarket setting.

Adoption of a New Device, Feedback, and Continued Innovation

The adoption of a new device in widespread clinical practice does not signal the end of the development process. In fact, widespread use is typically a prerequisite for garnering insights about the technology that provide important feedback to the R&D sector, either in industry or academia, about necessary improvements to optimize ease of use and the associated outcomes. These second-generation devices then re-enter the cycle of preclinical and clinical evaluative studies.

Ongoing innovation, however, does not only take place in R&D laboratories, but also in clinical practice itself. A common phenomenon is that, with further experience, improved strategies of managing patients with a device may emerge, including changes in the operative intervention, postoperative management, and outpatient care. In addition, the selection of

patients tends to change and expand. An interesting example can be found in laparoscopic surgery. Consider the transition from open surgical procedures to minimally invasive surgical approaches. These laparoscopic procedures tend to minimize post-operative pain and recovery time, and may reduce the treatment cost per patient. As a result, the target population for these procedures has expanded. Often this includes less sick patients for whom the risks of the procedure are now acceptable or sicker patients who initially were too risky to be candidates. This potential to expand the target population suggests that elasticity of demand for medical services is greater than commonly supposed.

In addition, totally new indications for use may emerge from the application and mastery of seemingly routine practices. Most medical devices achieve new indications by transfer from one organ system to another, although these transfers often require design modifications. The first endoscopes, for example, were used for cystoscopy early in this century. In the 1960s, after the development and introduction of fiber-optics, gastrointestinal endoscopy and gynecological laparoscopy became well established. A further extension of endoscopy depended on the eventual joining of television cameras to the scope, which facilitated their use in procedures such as arthroscopy. Widespread use is often a precondition for identification of these new uses, and clinical practice itself is a central source of medical innovation. "Learning by doing" in clinical practice, which may suggest modifications in the technology and the design of confirmatory trials, is widespread and confers broad health and economic benefits. A study of the top 20 blockbuster drugs from 1993 found that secondary indications exceeded 40 percent of revenues, and that a similar pattern held for medical devices (Gelijns et al., 1998)

Postmarket Evaluation

There are various reasons, as suggested above, why it is important to collect outcomes data in the postmarket setting. Premarket trials have limited time frames and seldom measure long-term effectiveness or safety. In pediatric clinical trials, the long life expectancy of children offers ample opportunity for late consequences of a disease, or treatment, to develop, which may be unknown at the time of treatment. The delayed consequences of radiation treatment of the face for teenage acne, for example, were only seen decades after treatment as an increased incidence of thyroid cancer. Trials also intentionally limit patient heterogeneity and, therefore, may not be generalizable to all potential recipients, who will receive the device in the postmarket setting. Moreover, premarket trials are often conducted in specialized centers, and as the device disseminates to other participants, the outcome parameters may change.

The iterative nature of medical device development argues for continued monitoring of devices as they are used in general clinical practice. There are various ways in which postmarket data can be collected. Mandatory and voluntary reporting of device-related deaths and serious adverse events to the FDA by manufacturers and clinicians has been plagued by underreporting. As part of the voluntary reporting system, the FDA has been implementing the MedSun system since 2002, an Internet-based pilot reporting system, comprised of over 180 hospitals and nursing homes.

The FDA could also mandate more postmarket studies or registries as part of the PMA approval. Clinical trials in the postmarket setting may differ substantially from premarket studies in their target populations, endpoints, and comparison groups. While FDA-related trials in the premarket setting may utilize a placebo control group (although not often with devices), postmarket studies are more concerned with comparisons between alternative treatment options. Postmarket studies are more apt to use a general practice setting than "centers of excellence" and to expand the target population beyond those seen in premarket studies. Moreover, they are more likely to include a broader range of outcomes, including functional status, quality of life, and economic endpoints facilitating much more accurate and meaningful estimates of the cost-effectiveness of new treatment options.

Specialty societies or regional authorities might also independently initiate such registries. For example, consider ECMO or extracorporeal life support (ECLS), which is a modified form of cardiopulmonary bypass, used in children and adults (Zapol et al., 1979). As the use of ECMO gained in popularity in 1984, the Neonatal ECMO Registry was established and began collecting data on in-hospital outcomes from clinical centers. To date, ECLS has been employed in more than 26,000 neonatal and pediatric patients with an overall survival rate of 68 percent (Lequier, 2004). In the United Kingdom, clinical trials are now being conducted to assess the long-term outcomes of ECMO. Another case in point is the New York State Cardiac Advisory Committee, which required all hospitals in New York State to collect data on the in-hospital outcomes for pediatric patients undergoing surgery to correct congenital cardiac defects. The risk-adjusted outcome rates for the specific hospitals can be used in quality improvement programs. Generally speaking, either hospitals or the device manufacturers conduct these postmarket observational studies. A more recent model of postmarket data collection involves LVADs. As a condition of marketing and reimbursement approval of the HeartMate™ LVAD for destination therapy (long-term implantation) in patients with advanced heart failure, the manufacturer must collect long-term data on patient outcomes and device performance for all patients receiving the implant. Three major government agencies (FDA, CMS, and NIH) have put for-

ward funds to support the registry, which would be coordinated by an independent organization. The participating hospitals would provide in-kind support for data collection efforts, while industrial firms would provide additional financial support. The expectation is that industrial firms would assume the responsibility for the registry over time. Models like this might provide interesting formats for the pediatric device world where private sector funds are limited.

CONCLUDING OBSERVATIONS

Incentives for innovation in the area of pediatric devices are far less compelling than for the adult population. Generally speaking, this area is characterized by small markets, limited reimbursement, and formidable challenges to conducting premarket trials. The perception is that these obstacles have resulted in unmet needs for diagnosing and treating diseases in children. Many diseases could benefit from improved or novel devices (such as pediatric LVADs for cardiomyopathies). Although, in some areas, the demand has been partially met by clinicians modifying adult devices for use in children (such as the use of adult biliary stents for pediatric intravascular placement); this process is affected by the risk of little oversight of good manufacturing practices. Federal agencies have called for more data collection to better assess these unmet needs.

Although the extent of the problem is not defined in detail, expert opinion indicates that a strong case can be made for stimulating clinical innovation (including device innovation) in pediatrics (FDA, 2004b; see also AAP et al., 2004). Such innovation could lessen the substantial emotional and economic toll imposed by childhood diseases. However, as this paper argues, there is an equally strong case to be made for a more rigorous knowledge base about the effectiveness, safety, and economic impact of device modalities for children. Premarket clinical trials are limited in their ability to provide insights about long-term effectiveness and safety, resulting in uncertainty about the ultimate value of these devices. Moreover, this uncertainty is exacerbated by the fact that devices keep evolving long after they have moved out of the clinical development phase into widespread clinical practice itself. Observations by users about the limitations of devices are fed back into the R&D process and may lead to subsequent modifications. In addition, physicians modify the clinical management strategies for their device patients (e.g., implantation techniques, infection prevention techniques, or means to diminish bleeding), and change the selection criteria for patients eligible for device therapies. This evolution, which is largely based on tacit know-how and usually not subjected to formal experimental testing, further heightens the uncertainty level about the clini-

cal and economic impact of devices, and, hence, our understanding about best practices in caring for patients.

Yet, there is a tension between stimulating innovation and increasing the requirements for collecting more data on the clinical and economic impact of device therapies, which is exacerbated by the small size of many of the markets and affected patient populations. Attempting to eradicate all clinical uncertainty in the premarket phase is impossible, and attempts to bring the level of uncertainty down to minute levels would be costly in terms of the time and expense of the premarket development process, not to mention the indirect expense of holding off a promising therapy from patients. Diminishing these uncertainties requires widespread clinical use and ongoing outcomes assessment in the postmarket setting. However, even if we emphasize postmarket data collection, we need ensure that this in itself does not impose an additional disincentive to pediatric device innovation.

What then are some of the options for achieving this? Facilitating the process of premarket and postmarket trials requires solutions that lie within the analytical, institutional and financial realms. First of all there are various ways of decreasing the sample size for premarket clinical trials. This is important because, in general, pediatric disease populations are small enough that enrollment times would be lengthy and threaten the usefulness and validity of the results of the trial as well as drive up the related costs. Techniques such as Bayesian analysis, which utilize prior probabilities in the hypothesis testing, relaxing the tolerance to random variation error (i.e., utilizing more relaxed confidence intervals), or utilizing non-concurrent control groups and objective performance criteria, each can reduce the required sample size compared to a classic randomized controlled trial. Another consideration is to eliminate requirements for extensive premarket studies in children when the device in question has been used widely in adults, the pathophysiology of the disease is similar in adults and children, and the adaptation of the devices requires no major technological changes (FDA, 2004b).

Another important set of initiatives can be found in the institutional realm. We need to strengthen the institutional infrastructure for conducting clinical trials for devices in pediatrics by creating networks of pediatric hospitals. A case in point is childhood cancer, which constitutes a fairly small population. Nearly 95 percent of children with cancer under age 15 are treated at institutions that are affiliated with the Children's Oncology Group, resulting in more than 70 percent of cancer patients in this age group being enrolled in one or more clinical trial (Tejeda et al., 1996; Bleyer et al., 1997). Although the group focuses on evaluation of multi-modal cancer therapy (i.e., effective use of combinations of surgery, radiation, and chemotherapy), this network, with appropriate public or private funding,

may be used for evaluation of surgical, radiological, and drug delivery devices. These U.S. hospital networks should also become involved in data collection in the postmarket setting, which requires better integration of data collection for these studies with the data collection systems used in everyday practice of medicine. These institutions could be induced to participate through better reimbursement rates for the care they provide or through direct subsidy for data collection efforts by research agencies. The NIH, for example, sponsors the pediatric heart disease clinical research network to study new interventions for congenital heart disease.

This brings us to the financial realm. There is an increased need for public–private partnerships for funding premarket trials of innovative pediatric devices (as per the philosophy of the NIH Roadmap) and postmarket studies. The products of this research are subject to the classic public good argument, where health benefits would accrue to the public-at-large, but investors would be unable to derive a sufficient return on their investment. Alternatively, one could also argue for increasing the financial incentives to the private sector, which would be able to raise private funds for developing and evaluating novel pediatric devices. Among suggested incentives are decreased or capped liability or better reimbursement for pediatric device therapies.

The need to obtain better knowledge about the clinical and economic impact of devices, especially in the postmarket setting is a general one. The pediatric case, however, offers unique challenges in that the incentives to innovate are weak as a result of small populations, which also complicates the clinical trial process. Therefore, the case is especially strong for the creation of novel partnerships between the public and private world that would experiment with new analytical, institutional, and economic models.

REFERENCES

AdvaMed. 2004. The Medical Technology Industry at a Glance. Available at: http://www.advamed.org/newsroom/chartbook.pdf. Accessed 11/15/04.

American Academy of Pediatrics (AAP), Ambulatory Pediatric Association (APA), American Pediatric Society (APS), et al. 2004 (August 20). Letter to Food and Drug Administration re: Response to FDA's Request for Comments on the Availability of Appropriately Designed and Adequately Studied Medical Devices.

Bartlett RH, Andrews AF, Toomasian JN, et al. Extracorporeal membrane oxygenation for newborn respiratory failure: forty-five cases. *Surgery* 1982;92:425–433.

Bleyer WA, Tejeda H, Murphy SB, et al. National cancer clinical trials: children have equal access; adolescents do not. *J Adolesc Health* 1997;21:366–373.

Centerwatch, Clinical Trials Listing Services. Available at: http://www.centerwatch.com/. Accessed 3/10/05.

Department of Health and Human Services (DHHS). Statement by R Pettigrew on FY 2005 NIBIB Budget Request. Available at: http://www.hhs.gov/budget/testify/b2004040ln.html.

Drotar, D. (ed). 1998. *Measuring Health-related Quality of Life in Children and Adolescents: Implications of Research and Practice*. Mahwah, NJ: Lawrence Erlbaum Associates.

Eiser C, Morse R. Quality of life measures in chronic diseases in childhood. *Health Technol Assess* 2001;5(4).

Feigal DW, Gardner SN, McClellan M. Ensuring Safe and Effective Medical Devices. *N Engl J Med* 2003;348(3):191–192.

FDA (Food and Drug Administration), Office of Device Evaluation. 1992. *Annual Report Fiscal Year 1992*. Rockville, MD.

FDA, Center for Devices and Radiological Health. 2001. *Humanitarian Device Exemptions: Questions and Answers; Final Guidance for Industry*. Available at: http://www.fda.gov/cdrh/ode/guidance/1381.html. Accessed 11/12/04.

FDA. 2004a. New Humanitarian Device Approval: Vertical Expandable Prosthetic Titanium Rib (VEPTR)–H030009. Available at: http://www.fda.gov/cdrh/mda/docs/h030009.html. Accessed 10/20/05.

FDA. 2004b. *Report to Congress: Barriers to the Availability of Medical Devices Intended for the Treatment or Diagnosis of Diseases and Conditions That Affect Children*. Washington, DC: FDA. Available at: http://www.fda.gov/cdrh/pediatricdevices/rtc100104.html. Accessed 07/08/05.

Freedonia Group. 2003. US Implantable Medical Device Demand to Exceed $24 Billion in 2007. Available at: http://www.the-infoshop.com/press/fd161115_en.shtml. Accessed 3/8/05.

Gelijns AC. 1991. *Innovation in Clinical Practice: The Dynamics of Medical Technology Development*. Washington, DC: National Academy Press.

Gelijns AC, Rosenberg N. The dynamics of technological change in medicine. *Health Affairs* 1994 Summer;13(3):28–46.

Gelijns AC, Rosenberg, N. 1999. Diagnostic Devices: An Analysis of Comparative Advantages. In Mowery D, Nelson R (eds). *The Sources of Industrial Leadership in Seven Industries*. Boston, MA: Cambridge University Press. Pp. 312–358.

Gelijns AC, Thier SO. Medical innovation and institutional interdependence: Rethinking university-industry connections. *JAMA* 2002;287(1):72–77.

Gelijns AC, Rosenberg N, Moskowitz AJ. Capturing the unexpected benefits of medical research. *N Engl J Med* 1998;339(10):693–698.

Koot HM, Wallander JL. 2001. *Quality of Life in Child and Adolescent Illness*. East Sussex: Brunner-Routhledge, New York:Taylor and Francis, Inc.

Lequier L. Extracorporeal life support in pediatric and neonatal critical care: A review. *J Intensive Care Med* 2004;19(5):243–258.

Lewin Group. 2000. *Outlook for Medical Technology Innovation: Will Patients Get the Care They Need? Report 1, The State of the Industry*. The Health Industry Manufacturers Association.

McClellan MB, Tunis SR. Medicare coverage of ICDs. *N Engl J Med* 2005;352(3):222–224.

Moskowitz AJ. 2003. Report of the Panel on the Medical Devices and Equipment Industry. In: *The Impact of Academic Research on Industrial Performance*. Washington, DC: National Academy Press. Pp. 77–114.

Moskowitz AJ, Reemtsma K, Rose EA, Gelijns AC. 1997.Clinical Outcomes in Surgery. In: Sabiston DC, Lyerly HK (eds.). *Textbook of Surgery: The Biological Basis of Modern Surgical Practice*. 15th ed. Philadelphia, PA: WB Saunders. Pp. 36–54.

National Academy of Engineering (NAE). 2003. *The Impact of Academic Research on Industrial Performance*. Washington DC: National Academy Press.

National Association of Children's Hospitals and Related Institutions (NACHRI). 2001. All Children Need Hospitals. Available at: http://www.childrenshospitals.net Accessed 11/12/04.

National Heart, Lung, and Blood Institute. 2002. *Report of the Task Force on Research in Pediatric Cardiovascular Disease*. Available at: http://www.nhlbi.nih.gov/resources/docs/pediatric_cvd.pdf. Accessed 3/9/05.

National Institute of Biomedical Imaging and Bioengineering (NIBIB). 2005. Untitled. Available at: http://www.nibib1.nih.gov. Accessed 6/17/05.

New York State Cardiac Advisory website. Available at: http://www.health.state.ny.us/nysdoh/heart /pediatric/message.htm. Accessed 3/9/05.

Rose EA, Moskowitz AJ, Packer MP, et al. The REMATCH trial: rationale, design, and end points. *Ann Thorac Surg* 1999;67:723–730.

Rose EA, Gelijns AC, Moskowitz AJ, et al. Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure (REMATCH) Study Group. Long-term mechanical left ventricular assistance for end-stage heart failure. *N Engl J Med* 2001; 345(20):1435–1443.

Rosenbaum PL, Saigal S. Measuring Health-Related Quality of Life in Pediatric Populations: Conceptual Issues. In Spilker B. (ed.). *Quality of Life and Pharmacoeconomics in Clinical Trials*. 2nd ed. 1996. Philadelphia, PA: Lippincott-Raven Publishers. Pp. 785–791.

Sansom W. Titanium rib becomes 1st new FDA-approved spine deformity treatment in 40 years. *HSC News, The University of Texas Health Science Center at San Antonio*. 2004;37(37):unpaged. Available at: http://www/uthscsa.edu/hscnews. Accessed 10/20/05.

Shaw BF. 1987. The Role of the Interaction between the Manufacturer and the User in the Technological Innovation Process. Ph.D. dissertation. University of Sussex, Sussex, United Kingdom.

Tejeda HA, Green SB, Trimble EL, et al. Representation of African-Americans, Hispanics, and whites in National Cancer Institute Cancer Treatment Trials. *J Natl Cancer Inst* 1996;88:812–816.

Trajtenberg M. The use of multivariate regression analysis in contrast-detail studies of CT scanners. *Medical Physics* 1984;11(4):456–464.

Tufts Center for the Study of Drug Development (TCSDD). Cost issues increasingly drive U.S. formulary and clinical guidelines. *Impact Report* 2004; 6(5).

Ungar WJ, Santos MT. The Pediatric Economic Database Evaluation (PEDE) project: establishing a database to study trends in pediatric economic evaluation. *Med Care* 2003; 41(10):1142–1152.

Von Hippel EA, Finkelstein SN. Analysis of innovation in automated clinical chemistry analyzers. *Sci Public Policy* 1979;6(1):24–37.

Wilkerson Group. 1995 (June). *Forces Reshaping the Performance and Contribution of the U.S. Medical Device Industry*. The Health Industry Manufacturers Association, Washington, DC.

Zapol WM, Snider MT, Hill JD, et al. Extracorporeal membrane oxygenation in severe respiratory failure. *JAMA* 1979;242:2193–2196.

D

Questions and Methods in Surveillance Programs

Stephen Lagakos, Ph.D. and William DuMouchel, Ph.D.**

This appendix reviews some technical aspects of the strategies that can be used after a medical device is marketed to assess its safety and efficacy or effectiveness. It begins by looking at various measures of interest in medical device surveillance, for example, the probability of an adverse event or the relative risk of experiencing an adverse event under different circumstances. It then discusses how these probabilities or other measures would be estimated with ideal information and how the actual data available to evaluators departs from the ideal. Particular attention is focused on analytic methods based only on numerator data (event counts) because these are applicable to many kinds of surveillance data. The last sections discuss different strategies, including disproportionality analysis, for evaluating device safety.

CHARACTERISTICS OF INTEREST

Probabilities of Outcome Events

An analysis of adverse device events should distinguish between events that are clearly identifiable as being due to a device (e.g., fracture of a cochlear implant) and those that can occur in individuals with the same disease or condition whether or not they have the device (e.g., development of meningitis in someone with a cochlear implant). Ideally, an analysis of

*Members, Institute of Medicine Committee on Postmarket Surveillance of Pediatric Medical Devices.

adverse event reports would also allow one to identify characteristics of a device user (e.g., gender, age, or disease severity) that might affect the probability of an adverse event.[1] Quantitatively, for adverse events (AE) that are clearly identifiable as being due to a device, the two probabilities (P) of interest (where Z is an individual characteristic) are

a. P[AE | device], and
b. P[AE | device, Z].

In contrast, for adverse events that could be due to the device or other causes (e.g., stroke in persons with aortic valve replacement; cf Ionescu et al., 2003), interest would more naturally focus on probabilities indicating the difference in risk for those with the device and those without, that is,

c. P[AE | device] versus P[AE | no device], and
d. P[AE | device, Z] versus P[AE | no device, Z].

As described below, different types of data structures would give rise to different strategies for comparing risks between individuals who do and do not have the device.

A full evaluation of the possible harms posed by a device should put harms in context. Thus, it should include information about the comparative probabilities of desired outcomes or benefit (e.g., reduced mortality, improved hearing, or cessation of tremor).

Associations Between Device Use and Outcomes

While the above probabilities represent the quantities we ideally would like to have to evaluate the safety of a device, the statistical association between use of a device and the probability of an adverse event or other outcome can be quantified as a function of these probabilities. One frequently used statistic, the odds ratio (OR), is a measure of the association between a device and an outcome, defined by

$$\text{OR}=\{P[\text{AE} \mid \text{device}]/P[\text{no AE} \mid \text{device}]\}/ = \{P[\text{AE} \mid \text{no device}]/P[\text{no AE} \mid \text{no device}]\}.$$

Thus, an odds ratio of 1 corresponds to no association between use of the device and the probability of an adverse event, while an odds ratio greater

[1]In practice, it is often also of interest to know the time from use of the device until the occurrence of an event, in which case the probabilities above would be replaced by the distribution function for the time until the event.

than (less than) 1 indicates that use of the device is associated with a higher (lower) probability of the event. As we see below, some types of studies enable the estimation of an odds ratio without being able to estimate the individual probabilities that comprise it.

When the probability of an adverse event is small, say less than 10 percent, the odds ratio is numerically similar to another statistic, relative risk (RR). This statistic is defined by

$$RR = P[AE \mid device]/P[AE \mid no\ device].$$

As with the odds ratio, a relative risk ratio of 1 corresponds to no association between use of the device and the risk of an adverse event. A relative risk greater than (less than) one corresponds to an increased (decreased) risk for those with a device. Thus, studies that permit estimation of the odds ratio can also estimate the relative risk when event rates are small. In some situations, as described below, another assumption can allow relative risk to be estimated without estimates of individual probabilities.

Ideally, each of the quantities described above could be estimated using appropriate numerator and denominator data. Depending on the probability of interest, the denominator might be the number of individuals with a medical condition and the numerator, the number of those in the group that had experienced an adverse device event. For other probabilities, the denominator might be those in the group who had a particular characteristic (e.g., being male) and the numerator, the number in that group who had experienced the adverse event.

Obtaining Numerator and Denominator Data

A variety of data collection strategies exist to obtain numerator and denominator data. One way of describing data capture mechanisms is based on whether they are "active" or "passive." Generally speaking, an active data collection system is based on an identified cohort of individuals (e.g., all children who did or did not receive a device at a particular hospital during a defined period of time) that is prospectively followed for the occurrence of the event of interest. Examples of such active strategies include clinical trials and prospective observational studies. Individuals are commonly evaluated for occurrence of the event periodically (e.g., proper functioning of the device) or a system for real-time reporting of adverse events exists. When well designed and implemented, these kinds of studies allow identification of both numerators and denominators of interest (although some individuals may be lost to follow-up).

In contrast, with passive data collection, a system allows events to be reported, but little or no effort is made to ensure that all events of interest are

reported. Usually, passive systems do not provide for reporting of denominator data (e.g., number of people at risk of a particular kind of adverse event).

For example, the U.S. Food and Drug Administration (FDA) requires health care facilities to report certain adverse device events to device manufacturers (and sometimes to the FDA as well), but no agency procedures, incentives, or other mechanisms exist to ensure that such reporting occurs. Even with perfect reporting, that system would not include denominator data, although such data might be collected or estimated in certain cases (e.g., if a manufacturer could provide reasonably complete information on patients implanted with a particular kind of device or if data from other sources allows reasonable estimates of the number of people with the relevant medical condition).

Such additional information can change the perspective on adverse event reports. In 2003, based on a number of adverse event reports, FDA issued a notice advising physicians that patients who had had a certain kind of drug-eluting stent implanted might experience a higher incidence of subacute thromboses and hypersensitivity reactions than those with bare metal stents (FDA, 2003). A year later, based on follow-up data from a required manufacturer postmarket registry and review of reports involving bare-metal stents, the FDA issued an update that concluded that the stent was not associated with a higher rate of subacute thromboses or hypersensitivity reactions (FDA, 2004). It also concluded that the reported rate of thromboses from the registry was not greater than the rate during the premarket clinical trials and that it was within the expected rate for any stent.

In some special instances, specific designs may be set into place for capturing certain events. For example, if there is a registry of all individuals that are diagnosed with a medical condition, what is called a case-control design (see below) can be used to match each individual reported to have an adverse event with a control. Then, data on characteristics (including whether a device was used) for both groups can be retrospectively evaluated from the registry to determine whether having the device is associated with the risk of the event. Alternatively, a case-cohort design could be employed in which characteristics of all individuals who have an event as well as characteristics of a random subset of those from the entire population are determined. The specific design will determine which aspects of the risk can be estimated. In a case-control design, the odds ratio can be estimated even though the individual probability of a device user (or person without a device) having an adverse event cannot be estimated.

Sources of Bias

The ultimate value of any surveillance system will depend critically on the bias and precision of the estimates it provides of the probabilities dis-

cussed above. The underreporting of events (numerator data) leads to underestimates of absolute risks and often to distorted comparisons, especially when the extent of underreporting varies depending on individual characteristics, for example, source of medical treatment. Bias may also occur when events that are not really related to a medical device are reported as adverse device events. For example, an incident may be reported as an adverse event for a particular device when the event was related to the patient's medical condition. This kind of "false positive" can result in overestimates of absolute risks and, again, distorted comparisons of groups. Such bias can be avoided by confirmation procedures for reported events. However, such confirmation can be difficult if the events are not being reported and confirmed in real time or, at least, reasonably close in time.

Biased estimates of risk can also arise from under- or overestimation of those potentially at risk of an event (denominator data). This is primarily a concern with passive data collection systems. Sometimes, however, information is being actively collected on people with a medical device but not on people without a device, so that both the number and characteristics of this group are unknown.

SPECIFIC STUDY DESIGNS AND INFORMATION RESOURCES

This section discusses several specific strategies for evaluating the safety and effectiveness of medical devices. Most of these strategies are employed to evaluate a device for purposes of securing FDA approval or clearance for marketing. They can also be used for surveillance (even if the purpose is not so described), and the discussion below cites examples of such use. The discussion begins with the randomized trial, which is widely regarded as the "gold standard" for evaluating clinical interventions, and then considers the others in general order of their perceived methodological soundness. For each design, we discuss (1) biases with respect to identification of target population, (2) biases from comparisons of individuals with and without device, (3) biases with respect to complete and accurate ascertainment of events, (4) biases with respect to duration of follow-up, (5) precision, (6) available measures of efficacy and safety, and (7) feasibility.

Useful information can be obtained in many ways, and for any study, potential sources of biases related both to the study design and its execution in practice should be considered. If FDA approval of medical devices were dependent on the types of trials typically offered in support of FDA approval of drugs, the hurdles to approval would be very high for both practical and ethical reasons.

Randomized Controlled Trials and Other Interventional Studies

Randomized comparative clinical trials, typically called Phase III trials in the world of pharmaceutical studies, are considered to be the most reliable scientific design for evaluating the safety and efficacy of an intervention. Ideally, a random sample of subjects is selected from a well-defined target population, and then subjects are randomly assigned to one of several interventions. Subjects are followed for the development of one or more desired outcomes (benefits) and for unwanted side effects (harms or adverse events). The key feature that sets randomized trials apart from other studies is the randomization, which is intended to eliminate bias in the selection of study subjects in the intervention and control groups. By chance, however, groups based on random assignment can differ in important ways. Therefore, researchers typically compare the groups to see whether they differ in significant ways on potentially relevant characteristics.

With appropriate planning, the size of the trial can be determined to yield the desired precision for estimating event probabilities and comparisons of intervention arms. As with any study, problems can arise in randomized trials that affect the validity or interpretability of the results. One is that the participants may have been properly randomized to control and intervention groups, but the participants themselves do not represent the target population. This could occur, for example, if the source of participants is not typical of the population, or if a substantial proportion of eligible subjects decline to participate. This would not affect the internal validity of the trial because patients that do participate are randomized. However, it could affect the degree to which the results can be generalized to the target population.

Biases can arise in randomized trials in several ways. Chief among these are ascertainment bias, bias due to nonadherence, and missing data/losses to follow-up. Ascertainment bias refers to differential criteria being applied in the evaluation of outcome variables, usually due to the knowledge of a subject's treatment group by the individual who evaluates the subject. This can often be prevented by either conducting a double-blind trial (in which neither the evaluator nor the subject is aware of the treatment arm), or by blinding the evaluation process. Nonadherence refers to subjects not receiving the interventions to which they are assigned. This can sometimes be a problem in trials that evaluate a drug that may be difficult to tolerate. In device trials, the main concern is that subjects receive the intervention (e.g., device or no device) to which they were assigned.

Follow-up and other types of missing data can diminish the power of a clinical trial and, more importantly, introduce bias in the comparisons of interventions. The latter can arise, for example, if subjects at greater (or lesser) risk of imminent failure leave the trial before their failure is observed. Yet another limitation of randomized clinical trials in some settings is there

might be ethical concerns about use of an untreated control group when there is some promising information available about the efficacy of a device.

Most randomized clinical trials allocate subjects among the intervention arms in a predetermined frequency, usually in equal proportions. However, allocation of subjects can also be done in an *adaptive* way, in which the allocation of future subjects depends on the outcomes of previously allocated subjects. One such approach is called randomized play-the-winner, in which assignment to one treatment or the other is randomized, but influenced by all the previous patients in the study. Statistical significance is reached when the difference between the numbers of patients randomized to the two groups becomes sufficiently large that it cannot be readily explained by chance. This feature of tending to allocate more patients to the superior treatment has advantages on ethical grounds.

In the 1980s, such a design was used to assess the efficacy of therapy involving extracorporeal membrane oxygenation (ECMO, also called extracorporeal life support or ECLS), a form of cardiopulmonary life support that involves an array of medical devices (e.g., vascular access catheters, blood pump, tubing, an artificial lung [often called an oxygenator]). The first child was randomly assigned (with 1 chance out of 2 of ECMO assignment) to ECMO therapy and survived; the next was randomly assigned (with 2 chances out of 3 of ECMO assignment) to conventional treatment and died. With the randomized scheme now more strongly weighted toward the option with the better result (with 3 chances out of 4 of ECMO assignment), the next patient received ECMO and survived, after which the next 10 patients in a row were assigned to ECMO. When all survived, the investigators were able to conclude on statistical grounds that ECMO was significantly superior to conventional treatment. Nonetheless, the unusual design led many in the medical community to question the results. At least two additional trials with more conventional designs were conducted in response to such skepticism.[2] Both

[2]Investigators in the next trial believed that the accumulating clinical results with ECMO were so superior to conventional treatment that a traditional randomized trial would be unethical (see account by Truog, 1999). They used a different adaptive randomization design that randomized patients evenly (50–50) to ECMO or conventional treatment until one option accumulated four deaths, after which patients were assigned to the more successful arm until the difference between groups reached statistical significance. After ten patients had been assigned to conventional therapy, four had died; the first nine patients assigned to ECMO survived. The next 20 patients received ECMO with one death. As observed by Truog, "In retrospect, four patients died who might have survived if they had been offered ECMO. Nevertheless, this was a smaller number than would have died if the trial had been designed with traditional 50/50 randomization. To this extent, adaptive randomization was successful in both demonstrating the superiority of ECMO and in reducing the total number of deaths" (Truog, 1999). Subsequently, investigators in the United Kingdom, who believed that a traditional trial was required, conducted such a trial until a monitoring body stopped the trial after 54 of 92 infants in the conventional treatment arm died compared to 30 of 93 in the ECMO arm (UK Collaborative ECMO Group, 1996).

supported the findings of the first trial. Because adaptive designs have the potential of assigning more subjects to the better intervention arm, they provide an attractive alternative in some settings.

There are many other variants of study design for randomized controlled trials, most requiring modifications in statistical analyses. In some studies, for example, individuals in randomly assigned intervention and placebo groups "cross over" at some point so that the intervention group is switched to the placebo and vice versa. One feature of such a design is that study subjects can, in essence, serve as their own controls (assuming that the effects of the intervention stop when the intervention stops).

Study subjects can also serve as their own controls in other ways. For example, a device might be studied in one eye with the other eye serving as a control (assuming baseline comparability of the eyes and no "spillover" effect of treatment). For some electrical stimulation devices, an individual's response is studied with the device on and with the device off.

Other studies involve comparisons of an individual's status following treatment to her/his status prior to receiving the intervention, which can create problems if a steady state of the condition—absent the intervention—cannot be assumed. Additional sources of bias can arise from a placebo effect and from incomplete data due to patient drop-outs.

A still weaker design involves comparisons with historical controls. For example, investigators may recruit individuals for an experimental intervention and then compare outcomes for this group with previously published outcome data on individuals who received alternative therapy. The choice of historical or retrospective controls presents various opportunities for bias as described below.

Prospective and Retrospective Cohort Studies

Prospective cohort studies may have as their goal the comparative assessment of two different interventions when the choice of intervention (e.g., method of contraception) belongs to the study subjects rather than the investigators. Subjects from a defined population, as well as the intervention they choose to take, are identified and followed over time to assess safety and efficacy. In this sense, prospective observational studies are similar to randomized trials. They thus share some of the benefits of trials, especially with respect to their prospective nature and can suffer from the problems caused by nonadherence and missing data/losses to follow-up.

The most important difference between a randomized trial and a prospective, comparative observational study is that interventions are determined at random in the former. When the intervention is determined by the subject or their caregiver, the opportunity for selection bias arises, and there have been many examples where this has led to misleading conclu-

sions. A likely recent example is the Women's Health Initiative, which demonstrated an increased risk of certain cardiovascular outcomes among women receiving estrogen therapy, when previous observational studies showed no evidence of increased risk, and in some cases a protective effect (Manson et al., 2003).

One potential advantage of a prospective, comparative cohort study is that it may not pose the ethical concerns about investigator assignment of study subjects that arise with some randomized trials. Another advantage is that enrollment of subjects or participants can be easier for prospective observational studies. As a result, they can be much larger and therefore have greater power to detect small differences in efficacy and adverse event rates between the comparison groups.

Retrospective cohort studies have similarities to prospective observational studies, but are constructed using individuals who have received an intervention (or not) in the past. The opportunity for biases in these studies is typically somewhat greater than in prospective observational studies. In particular, it can be more difficult to retrospectively identify and obtain follow-up information on subjects than when an observational study is conducted prospectively. In some cases, new information can be obtained from subjects about their status (outcomes).

Case Control Studies

Case control studies are based on the identification of samples from a population of subjects who have (cases) or have not (controls) experienced the adverse event and for whom the presence or absence of device use can be identified. Unlike randomized clinical trials and prospective or retrospective cohort studies, case-control studies cannot be used to estimate the probabilities of interest given in (a) and (b) above, but do provide estimates of the OR for assessing association between device use and outcome.

The validity of case-control studies depends on the selection of "cases" and "controls" who are representative of the populations of all subjects that did and did not experience the event, respectively. The selection of appropriate controls, in particular, can be challenging. The validity of case-control studies also depends on the accurate ascertainment of the intervention and other risk factors that might be associated with the outcome event. For many devices, ascertainment of whether or not a subject used the device can be reliably determined. Yet other risk factors for the event that might be used in multivariate analyses of association may depend on recall, and thus introduce bias.

An important advantage of case control studies is that they can more easily assess the association between a device or risk factor and a rare outcome than a prospective study. This is facilitated if registries of certain

types of events, such as a diagnosis of cardiomyopathy, are routinely maintained, for then a relatively large number of cases can be readily obtained and matched with controls to identify possible risk factors for the outcome. Also, event reporting systems, such as the MedSun system currently being implemented by the FDA, lend themselves to case-control studies to identify possible safety concerns with devices, provided that there is a means of selecting controls to match the cases and to ascertain the "exposure" status (e.g., device use or not) of both cases and controls.

Registry-Based Studies

A registry is a system for collecting information about a class of individuals or patients who have in common a disease, injury, condition, medical procedure or product, or similar characteristic or exposure. A registry study is an investigation that uses registry data alone or in combination with other data. Some registries are based on diagnoses and include information about people with that diagnosis who receive certain interventions and people with the diagnosis who do not. Other registries include only individuals who have received a device or intervention. The former approach is most useful for comparative studies of those who have and have not been treated with a device. In some cases, the registration consists only of limited information about the subject at the time the device was first used. In more elaborate settings, registrants are prospectively followed for outcome events, forming a prospective observational study.

DISPROPORTIONALITY ANALYSES OF SPONTANEOUS ADVERSE EVENT REPORTING DATABASES

An adverse event reporting system is not a study design as such. Adverse event reports can, however, be combined with information from simple registries or other data sources to conduct case-control studies.

Recently, new techniques for analyzing event databases have been gaining attention, mostly in the pharmaceutical arena. The remainder of this appendix reviews the application of these techniques to drugs and provides an example of an application to device databases.

Overview

Disproportionality analyses are the most common technique for analyzing adverse drug reaction databases, and they can also be used for analyzing adverse device events. They are a means of assessing the association between use of a device and outcome when denominator data are not available for estimating population parameters, as is the case with adverse

event databases. The risk of a particular adverse event (AE_1) can sometimes be assessed with only numerator data if there are also numerator data available for another adverse event (AE_2) that is not associated with use of the device. The rationale is to treat those experiencing the second adverse event as if they were the control group in a case-control study of the first adverse event (and vice versa). To see this, suppose that n_1 and n_2 denote the number of device subjects that experience AE_1 and AE_2, respectively, and that the unknown population size of device users is N. Similarly, let m_1 and m_2 denote the number of non-device subjects that experience AE_1 and AE_2; M denotes the unknown population size of non-device users. The *RR* corresponding to use of the device is

$$RR=(n_1/N)/(m_1/M) = [(n_1/n_2)/(m_1/m_2)]/ [(m_2/M)/(n_2/N)].$$

If use of the device is not associated with AE_2, we would expect approximately that $n_2/N = m_2/M$. Thus, we see that under these circumstances, the *RR* for association between device use and AE_1 can be estimated by

$$\text{RR} = (n_1/n_2)/(m_1/m_2).$$

Note that this expression for the *RR* depends only on numerator data (event counts) for the two types of adverse events and for subjects who do and do not have the device. Thus, the RR can be approximated based only on numerator data. As discussed below, key challenges in disproportionality analyses include accurately ascertaining the numerator counts n_1, n_2, m_1, m_2 and the assumption that the device is not associated with the risk of AE_2. In practice there are not just two adverse events involved in the analysis, but hundreds or thousands of different adverse events (so that AE_2 above represents the amalgamation of all events but AE_1), and it is generally assumed that the majority of the "other" events (as of all events) will not be associated with any particular device.

There are several important advantages of disproportionality analyses. Data from clinical trials are rarely plentiful enough for useful studies of rare adverse events, in which case it may be necessary to fall back on retrospective studies. A carefully planned and executed case-control study, in which ascertainment of cases is well documented and the choice of controls is appropriate, is highly desirable but expensive and time-consuming. It would usually only be used to study a rare adverse event for a particular device if there has been some existing evidence of a potentially serious problem with that device-adverse event combination. In order to uncover potential problems in the first place, we are almost

forced to fall back on anecdotal evidence and the analyses of databases of spontaneous reports.

The FDA, device manufacturers, and some other organizations maintain voluminous databases of spontaneously reported adverse events, consisting of coded and uncoded text descriptions of the patient, the device, what happened to the device, and what the effect of the adverse event was on the patient. These reports are typically not research quality in that the data collection or reporting guidelines and forms provided FDA are not equivalent in precision to those associated with formal studies, and the quality of provider, professional, and patient reports to manufacturers and FDA is highly variable Underreporting of adverse events is significant, and case-by-case follow-up may be necessary to correct reporting errors to confirm the existence of a problem. These are numerator data only, with no obvious way to match the report counts for each device-adverse event combination to an appropriate measure of exposure. In spite of the deficiencies of such data, analyses of frequency counts of spontaneous reports have proven useful as a problem screening and signaling tool in the adverse drug reporting domain.

Analytic Issues and Strategies

The idea behind disproportionality analysis is similar to the *proportional mortality analysis* of epidemiology, which might, for example, study a sample of death certificates and compare the distribution of deaths due to various causes for decedents who had different occupations. This is also a numerator-only analysis and is viewed as an outdated technique by most modern epidemiologists. Nonetheless, although such a study cannot measure the probabilities defined in (a) and (b), the measurement of associations between adverse events and drugs in databases can give (possibly biased) clues to problems during the postmarket phase. During this phase, the number of patients exposed to a new drug may grow by several orders of magnitude compared to the premarket phase, allowing much greater opportunity for rare events to be manifest.

Number of Reports	Mentioning AE	Not Mentioning AE
Mentioning Drug	$n = a$	b
Not Mentioning Drug	c	d

Suppose that the reports in a database are classified into the above 2×2 table, as to whether or not a particular drug and a particular adverse event are mentioned in a report. It is common to denote the counts of the four cells of a 2×2 table by the letters a, b, c, d, but we will sometimes use

the letter *n* to denote and emphasize the count in the first cell, where both the drug and the adverse event are present. The disproportionality measures are all of the form *n/e*, where *e* is a baseline or comparator value that is expected to be near *n* if the drug and the adverse event are not associated. Three variations in the definition of *e* are commonly used in disproportionality analyses:

$ROR = ad/bc$	$[e = bc/d]$
$PRR = [a/(a + b)]/[c/(c+d)]$	$[e = c(a+b)/(c+d)]$
$RR = [a/(a+b)]/[(a+c)/(a+b+c+d)]$	$[e = (a+b)(a+c)/(a+b+c+d)]$

ROR is the reporting odds ratio (Rothman et al., 2004), *PRR* is the proportional reporting ratio (Evans et al., 2001), and *RR* is the relative reporting ratio (DuMouchel, 1999). Note that the epidemiology literature commonly uses the abbreviation *RR* for "risk ratio," whereas in the literature analyzing spontaneous reports the preferred phrase is "reporting ratio," since the presence of noncausal associations is common in spontaneous reports. If the particular adverse event is relatively rare in the database, and the particular drug is also mentioned in a small proportion of the reports, then $a << b$, $c << d$ and all three measures *ROR, PRR,* and *RR* will be numerically similar. (It is very common for *a* to be less than 1 percent of *b* and *c*, and for these to be less than 1 percent of *d*, since the database may include thousands of different drugs and adverse events.) Of the three, *RR* has the computationally convenient property that whenever $n = a$ is greater than 0, *e* is also positive, so that the ratio *n/e* is well defined in all cases. For *ROR*, if $b = 0$ or $c = 0$, and for *PRR* if $c = 0$, then $e = 0$, leading to an undefined value of *n/e*. On the other hand, Rothman and colleagues (2004) point out that in those cases in which the condition $a << b$, $c << d$ (where << means "much less than") is not true, the odds ratio measure *ROR* has the advantage of avoiding certain biases that may be due to different drugs (or different adverse events) having different reporting rates. (Indeed, this is just why the odds ratio is the usually preferred measure of association for case-control studies.)

Returning to the rare-item situation where the values of *ROR*, *PRR*, and *RR* are all about equal, the value *n/e* has a natural interpretation as a multiplicative measure, the factor by which the number of observed cases exceeds the number expected under the null hypothesis of no association between the drug and the adverse event. Use of these measures can be severely hampered by several problems, including confounding with demographic or other variables and high sampling variance. To give an example of the former problem, consider the discussion of DuMouchel (1999) about the association of SIDS (crib death) and many vaccines. This is due to the fact that SIDS only occurs in infants by definition and that infants also

receive a high proportion of vaccines. If the database is restricted to reports involving infants, the associations disappear. Another example is the association between Viagra use and various cardiac events—due to the association of both of these items with age and gender, each being most common among elderly men. Similarly in a database spanning many years of reports, any drug very new to the market is more likely to show an association with an adverse event that is newly defined in MedDRA (Medical Dictionary for Regulatory Activities), the coding dictionary for adverse events used in most such databases. To combat these common confounding biases, it is recommended to stratify the database reports by gender, age of patient and year of report (and possibly other variables, if available) and to compute a version of the disproportionality measure that adjusts for stratum effects. This correction for demographic and secular trend confounding seems to be most often used with the measure *RR*. The correction in this case, originally due to Mantel and Haenszel (1959) consists of computing *e* separately for the reports within each stratum, and then summing the stratum-specific values to get a total *e* to use in the ratio *n/e*. There are also analogous ways to adjust ROR and PRR for stratum effects.

A trickier type of confounding is with the presence of an indication for taking the drug. For example, a drug used to combat cancer might have a reported AE that is a symptom of the cancer for which the drug is prescribed. It would be very difficult to automatically eliminate all such confounding from a computer database analysis. So far, the only feasible approach is to rely upon the medical knowledge of the analyst to recognize and discount such computed associations.

Another problem with disproportionality measures is their often extremely large variance. For example, a database analysis may find tens of thousands of drug–event combinations in which $n = 1$ and $e < 0.001$ so that $n/e > 1000$. In contrast, a value of $n = 20$, $e = 2$, $n/e = 10$, is usually going to be a much more "interesting" drug–event combination on which to follow up. There are two statistical approaches to controlling false positives due to the high variance of *n/e*. The first is to restrict computation of the disproportionality ratio to combinations in which some measure of statistical significance meets a threshold. For example, Evans and colleagues (2001) recommend restricting *PRR* to combinations in which $n > 2$ and the chi-squared statistic for association in the 2×2 table is at least 4. The second strategy is to use a Bayesian or empirical Bayesian analysis to produce "shrinkage estimates" that stabilize the ratios by applying a prior distribution that reduces ("shrinks") the ratios *n/e* when *n* and/or *e* are small. Bate and colleagues (2002 and references therein) describe a "Bayesian confidence propagation neural network" (BCPNN) method that has been used to analyze World Health Organization databases. The development and use of an empirical Bayes model, the "multi-item

gamma-Poisson shrinker" (MGPS) is described in DuMouchel (1999), DuMouchel and colleagues (2001), O'Neill and Szarfman (2001), Szarfman and colleagues (2002), and Fram and colleagues (2003). The latter system is in use at the FDA and several pharmaceutical manufacturers. These strategies have proven to be effective ways to reduce the noisiness of the disproportionality measures, but the role of such analyses in drug safety signaling is still evolving. Regulators and manufacturers are beginning to adopt them as an additional tool to help prioritize their pharmacovigilance efforts, but no one is proposing that they can provide definitive inferences without extensive follow-up.

Differences Between Drug and Device Adverse Event Data

There are several differences between drugs and devices that tend to change the potential use of spontaneous report databases. On the side of making reports regarding devices more useful, the more transparent action of many devices compared to a drug can often make even a single report very informative. For example, if a faulty device delivers an electric shock to the patient, physical inspection of the device might lead immediately to a suggested corrective design of the device—no reliance on statistical analysis is needed.

But there are other features of the device world that make it harder to use spontaneous report databases. There are more devices than drugs, and manufacturers modify the design of their devices much more frequently than drugs get reformulated. This means that a particular version of a typical device has a smaller user base than a typical drug, and thus a typically smaller number of reports in a database.

In addition, adverse event coding is more complicated for devices than for drugs, and not yet as standardized. A typical device adverse event report includes information both about what happened to the device as well as what happened to the patient, whereas the drug reports contain only the second sort of information. In the drug world, the MedDRA coding system has been adopted by the majority of collectors of adverse event reports around the world; no such standardization has been accomplished in the device world.

A device adverse event database might have several hundred thousand reports, with just a paragraph of narrative text describing what went wrong. A data mining approach would need to group the adverse event descriptions into at most a few thousand adverse event types, and preferably do this automatically, without the need for human review of each report individually. A computer analysis can try to form clusters of reports based on the common occurrence of words or phrases in the narrative. The automated discovery of which words or phrases are indicative of important

associations in the database is called *feature extraction*. But the feature extraction step introduces another layer of uncertainty into the analysis, and is usually less informative than being able to work with adverse event codes that fit a well structured theoretical framework.

The majority of drug adverse events have at least some natural background rate, making it seem natural to tabulate all combinations of drugs and adverse events in a data mining run. A user of practically any drug might conceivably show up with practically any adverse event, as diverse as liver damage and cardiac arrest.

The nonsystemic nature of many devices makes the universe of observed adverse events much more device specific. Does it make sense to tabulate the frequency of electric shocks for patients using blood vessel shunts, for example? If not, how do you automatically decide upon the universe of device–event combinations to tabulate and study statistically? Database analyses of device reports have not yet been attempted on anything like the broad scale of drug data mining methodology.

Example: Disproportionality Analysis for Spontaneous Reports of Shunt Complications

This section provides a short example of a disproportionality analysis for complications involving cerebrospinal fluid shunts that was used to support the discussion in Appendix E. The analysis used adverse event reports from the MAUDE database managed by ECRI (a private, nonprofit health services research organization). A preliminary group of 2,472 adverse event reports that seemed to involve cerebrospinal fluid shunts were selected. (The authors appreciate the assistance of Mark Bruley of ECRI in this process.) An attempt was made to classify the type of complication by computer scan of the descriptive narratives for certain key words (suggested by Dr. Stephen Haines, co-author of Appendix E). The 12 types of complications and the search words used for each type are listed in Table D.1.

The search for any of the text strings in Table D.1 was successful for just 784 of the reports. Table D.2 lists the counts of the manufacturer–event type combinations for these 784 reports. (The reports in which the shunt manufacturer was unknown are coded as "Man.I" in Table D.2.) The disproportionality analysis screens for unusually large counts (N) in Table D.2, in comparison to the count (E) that would be expected if there were no association between manufacturer and event type in Table D.2. In this example, the value of E for any event type and manufacturer combination is computed as the event type total times the manufacturer total divided by 784. The relative reporting ratio is defined as $RR = N/E$.

Table D.3 lists the 15 largest values of RR among the 108 potential event type and manufacturer combinations listed in Table D.2. Note that

TABLE D.1 List of 12 Shunt Complication Event Types and the Text Strings That Were Used to Classify the Reports in Searching the Descriptive Narrative in MAUDE Reports

Abdominal Cyst	"peritonitis," "pseudocyst," "pseudo-cyst," ("cyst" & "abdom"), ("cyst" & "periton")
Abdominal Metastas	"metastas," ("tumor" & "abdom"), ("tumor" & "periton")
Cardiac	"heart," "cardiac," "atri," "superior vena cava," "endocarditis," "vegetation"
Disconnection	"disconnect," "fracture"
Hemorrhage	"hemorrhage," "haemorrhage," "hematoma," "haematoma," "bleed"
Infection	"infect," "ventriculitis," "meningitis"
Malfunction	"malfunction," "occlu," "block," "obstruct," "plug"
Migration	"migrat"
Mortality	"death," "dead," "mortality"
Organ Perforation	"perforat," "penetrate," "extru"
Pneumocephalus	"air," "pneumocephalus"
Slit Ventricles	"slit," "intracranial hypotension," "overdrainage"

TABLE D.2 Counts (*N*) for a Classification of 784 Reports of Shunt Complication by Type of Event and Manufacturer

Event type	A	B	C	D	E	F	G	H	I	Total
Abdominal Cyst	2	0	0	1	0	0	0	0	0	3
Abdominal Metastas	1	0	2	1	0	0	0	0	0	4
Cardiac	2	0	1	1	0	0	0	0	2	6
Disconnection	15	0	4	91	3	0	0	3	9	125
Hemorrhage	24	2	4	7	10	1	1	4	1	54
Infection	29	0	8	20	3	1	0	2	9	72
Malfunction	123	5	23	137	35	6	1	11	39	380
Migration	3	0	1	0	6	0	0	0	1	11
Mortality	2	0	0	0	1	0	0	0	1	4
Organ Perforation	7	0	2	1	0	0	0	0	0	10
Pneumocephalus	3	0	3	0	0	0	0	0	0	6
Slit Ventricles	43	0	3	0	0	0	0	0	0	46
Total	254	7	51	259	58	8	2	20	62	721

SOURCE: ECRI MAUDE database.

TABLE D.3 The 15 Largest Reporting Ratios (*RR* = *N*/*E*) for Manufacturer–Event Type Combinations Listed in Table D.1

	Manufacturer Code	Event	*N*	*E*	*RR*	*EBGM*
1	Man. G	Hemorrhage	1	0.138	7.26	1.04
2	Man. C	Pneumocephalus	3	0.413	7.26	1.25
3	Man. C	Abdominal Mets	2	0.276	7.26	1.14
4	Man. E	Migration	6	0.982	6.11	1.70
5	Man. I	Cardiac	2	0.505	3.96	1.10
6	Man. B	Hemorrhage	2	0.551	3.63	1.10
7	Man. I	Mortality	1	0.337	2.97	1.01
8	Man. C	Organ Perforation	2	0.689	2.90	1.08
9	Man. E	Mortality	1	0.357	2.80	1.01
10	Man. C	Cardiac	1	0.413	2.42	1.00
11	Man. H	Hemorrhage	4	1.722	2.32	1.15
12	Man. A	Organ Perforation	7	3.240	2.16	1.24
13	Man. E	Hemorrhage	10	4.821	2.07	1.32
14	Man. A	Abdominal Cyst	2	0.972	2.06	1.04
15	Man. D	Disconnection	91	47.194	1.93	1.85

NOTE: The expected count *E* is computed under the assumption of no association between manufacturer and event type. The empirical Bayes geometric mean (*EBGM*) is a "shrinkage estimate" of *RR* that adjusts for the statistical uncertainty due to small counts. Note that the smallest value of *RR* in Table D.2 (Man. D, Disconnection, line 15) has the largest value of *EBGM* because it is based on much larger *N* and *E*.

the largest reporting ratios *RR* in Table D.3 have small values of *N*, but much smaller values of *E*. The ratio *RR* has a lot of statistical "noise" when such small frequencies are involved. The values of *RR* computed from such small counts cannot be expected to be very stable as more reports are received. These ratios can, however, be adjusted to discount or "shrink" large values of *RR* when they are based on such small counts. A statistical model, the empirical Bayes gamma-Poisson hierarchical model (DuMouchel, 1999) can produce improved estimates (called the empirical Bayes geometric mean, *EBGM*) of the "true" reporting ratio.[3]

These values appear in the final column of Table D.3. This model predicts that the combination (Manufacturer D, Disconnection) in line 15 of Table D.3, which has the lowest value of *RR* but is based on much larger

[3]Because relatively few reports were used in this analysis compared to adverse drug reaction data mining analyses, the empirical Bayes model used here was a simplification of that used in DuMouchel, 1999. The model used here assumes that the true relative ratio (True *RR*) has a prior distribution such that True *RR* = 1 with probability 1 – *P*, while, with probability *P*, True *RR* has a gamma distribution with parameters α and β. The analysis of the counts in Table D.2 resulted in the estimates $P = 0.50$, $\alpha = 3.79$, and $\beta = 3.85$, and these values led to the values of *EBGM* listed in Table D.3.

values of N and E than any other combination in Table D.3, actually has the largest "true" relative reporting ratio, $EBGM = 1.85$. A reporting ratio of 1.85 is interpreted as an estimated 85 percent excess frequency in disconnection reports for manufacturer D compared to the number expected if there were no association between manufacturer and shunt complication event type in the database. The reduction in estimated reporting ratios from RR to $EBGM$ is an attempt to adjust for the *multiple comparisons fallacy*. Since we examined nine manufacturers by 12 event types, we expect the largest of the $9 \times 12 = 108$ values of RR to be so large purely by chance. However, the statistical theory behind the shrinkage estimator $EBGM$ makes it safer (more valid statistically) to pick out the largest value of $EBGM$ without biasing the estimation of the reporting ratio. And, in fact, there have been literature reports of excess disconnections in shunts from manufacturer D.

REFERENCES

Bate A, Lindquist M et. al. 2002. A data mining approach for signal detection and analysis. *Drug Safety* 25(6):393–397.

DuMouchel W. 1999. Bayesian data mining in large frequency tables, with an application to the FDA Spontaneous Reporting System, *The American Statistician* 53:177–202.

DuMouchel W, Pregibon D. 2001 (August 26–29). Empirical Bayes screening for multi-item associations. *Proeedings of the Seventh ACM SIGKDD International Conference on Knowledge Discovery and Data Mining*, San Francisco, CA. Pp. 67–76.

Evans SJW, Waller PC, Davis S. 2001. Use of proportional reporting ratios (PRRs) for signal generation from spontaneous adverse drug reaction reports. *Pharmacoepia and Drug Safety* 10(6):483–486.

FDA (Food and Drug Administration). 2003. FDA Talk Paper: FDA Advises Physicians of Adverse Events Associated with Cordis Cypher Coronary Stents. Available at: http://boeree.hq.inverse.dk/bbs/topics/ANSWERS/2003/ANS01257.html. Accessed September 28, 2005.

FDA. 2004 (October 18). Public Health Web Notification: Final Update of Information for Physicians on Sub-acute Thromboses (SAT) and Hypersensitivity Reactions with Use of the Cordis CYPHER™ Sirolimus-eluting Coronary Stent. Available at: http://www.fda.gov/cdrh/safety/cypher3.html. Accessed September 28, 2005.

Fram D, Almenoff JS, DuMouchel W. 2003 (August 24–27). Empirical Bayesian data mining for discovering patterns in post-marketing drug safety. *Proceedings of the Ninth ACM SIGKDD International Conference on Knowledge Discovery and Data Mining,* Washington, DC. Pp. 359–368.

Ionescu A, Payne N, Fraser AG, Giddings J, Grunkemeier GL, Butchart EG. 2003. Incidence of embolism and paravalvar leak after St Jude Silzone valve implantation: experience from the Cardiff Embolic Risk Factor Study. *Heart* 89(9):1055-61.

Manson JE, Hsia J, Johnson KC, Rossouw JE, Assaf AR, Lasser NL, Trevisan M, Black HR, Heckbert SR, Detrano R, Strickland OL, Wong ND, Crouse JR, Stein E, Cushman M, the Women's Health Initiative Investigators. 2003. Estrogen plus Progestin and the risk of coronary heart disease. *New England Journal of Medicine* 349:523–534.

Mantel N, Haenszel W. 1959. Statistical aspects of the analysis of data from retrospective studies of disease. *Journal of the National Cancer Institute* 22:719–748.

O'Neill RT, Szarfman A. 2001. Some FDA perspectives on data mining for pediatric safety assessment. *Current Therapeutic Research, Clinical and Experimental* 62(9):650–663.

Rothman KJ, Lanes S, Sacks ST. 2004. The reporting odds ratio and its advantages over the proportional reporting ratio. *Pharmacoepidemiology and Drug Safety* 13:519–523.

Szarfman A, Machado SG, O'Neill RT. 2002. Use of screening algorithms and computer systems to efficiently signal higher-than-expected combinations of drugs and events in the US FDA's spontaneous reports database. *Drug Safety* 25(6):381–392.

Truog RD. 1999. Commentary: Informed consent and research design in critical care medicine. *Critical Care* 3(3):R29–R33.

UK Collaborative ECMO Trial Group. 1996. UK collaborative randomised trial of neonatal extracorporeal membrane oxygenation. *Lancet* 348(9020):75–78.

E

The Regulatory History of Cerebrospinal Fluid Shunts for Hydrocephalus

Stephen J. Haines, M.D., Jeffrey P. Blount M.D.***

STATEMENT OF PROBLEM

Cerebrospinal fluid (CSF) shunts are implantable devices inserted by neurosurgeons to treat hydrocephalus. Shunt insertion and revision are the operations most commonly performed by pediatric neurosurgeons (1). There is little question that these devices have saved the lives of thousands of children and reduced morbidity in tens of thousands more, yet CSF shunts demonstrate a substantially higher degree of failure or adverse outcomes than most approved devices in current use (2). The U.S. Food and Drug Administration (FDA) has regulatory authority over these and all medical devices. Historically the FDA has taken a limited regulatory approach toward CSF shunts. The purpose of this paper is to provide background about hydrocephalus and its surgical treatment and to examine the effect that such an approach may have had on the development, safety, and effectiveness of CSF shunts.

BACKGROUND AND DEFINITIONS

Anatomy and Physiology

Cerebrospinal fluid is continuously made (predominantly although not exclusively) within normal hollow cavities of the human brain called ven-

*Lyle A. French Chair, Professor and Head, Department of Neurosurgery, Professor of Pediatrics and Otolaryngology, University of Minnesota, Minneapolis, MN.

**Assistant Professor of Surgery, Department of Surgery, Division of Pediatric Neurosurgery, University of Alabama at Birmingham, Birmingham, AL.

tricles. The largest of the ventricles are the two lateral ventricles, which occur in parallel and have a shape that is complex but that can be broadly described as the appearance of a medially angulated letter C with a tail extending from their back (Figure E.1). The tail is the occipital horn while the top part of the letter C is the frontal horn and the inferior and more lateral part is the temporal horn. Smaller singular third and fourth ventricles are midline structures in direct communication with the lateral ventricles. At the base of the fourth ventricle in the brain stem (laterally out the foramen of Luschka and medially out the foramen of Magendie), the CSF escapes the middle of the brain and freely flows into the subarachnoid space that extends around the outside of the brain and down into the spine to surround the spinal cord and nerve roots.

Cerebrospinal fluid is generated by small fronds of pink-orange tissue within the ventricles called choroid plexus (Figure E.2). Blood flows into and out of the choroid plexus via the choroidal vessels, and the CSF is continuously generated from within the choroid plexus in an energy-dependent process. The rate of production of CSF is about 0.2–0.3 cc/

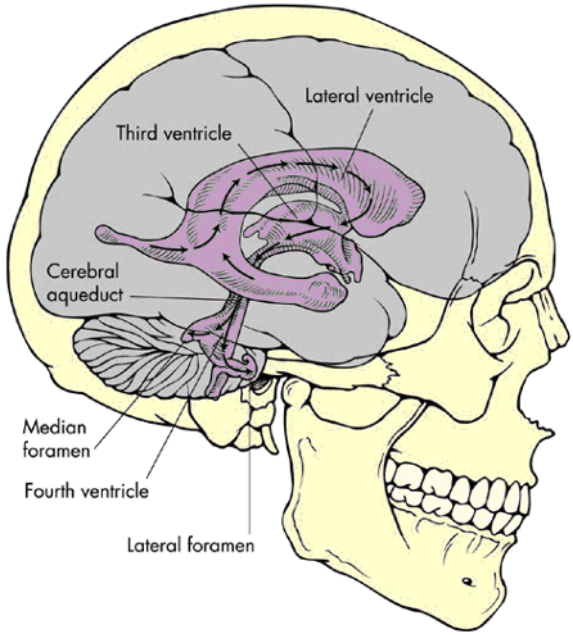


FIGURE E.1 Ventricles of the human brain (3). (Source: Brian J, Warner D. *Atlas of anesthesia: Scientific principles of anesthesia*. Miller R, Schwinn DA, eds., 1997. Used with permission of Current Medicine, Inc., via ImagesMD.com.)

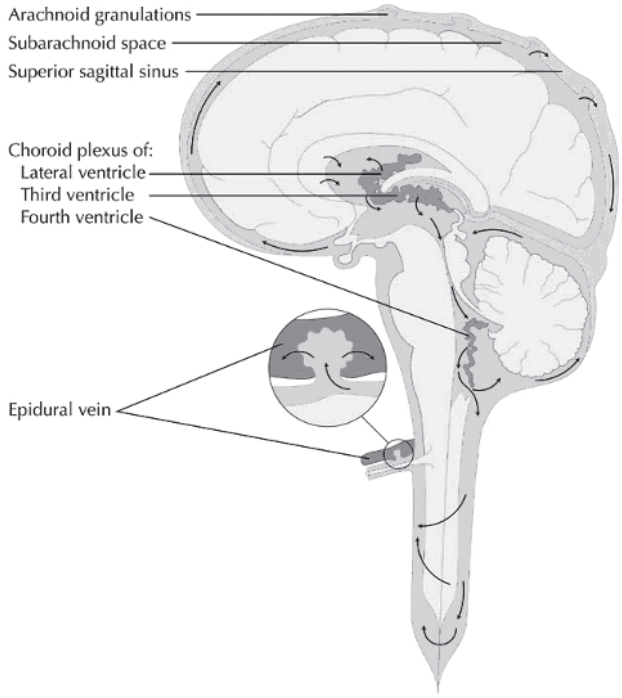


FIGURE E.2 The cerebrospinal fluid system (4). (Source: Digre K. Idiopathic Intracranial Hypertension Headache. *Current Pain and Headache Reports*. 6(3):217–225. Used with permission of Current Science, Inc., via ImagesMD.com.)

minute or 35 cc/hr. The total capacity of normal ventricles in adults or older children (above age 2) is about 35 cc, and another 120 cc of CSF surrounds the spinal cord and nerve roots. Thus, the total amount of CSF in the adult or large child is typically about 150–160 cc. Yet the rate of daily production of CSF is about 3 times that amount.

This imbalance is corrected by the resorption of CSF back into the bloodstream, which occurs primarily along the superior sagittal sinus and to a lesser degree from the epidural veins. Structures called arachnoid granulations (Figure E.2) extend extensively from the venous sinuses and serve to reabsorb CSF back into the bloodstream. As part of the plasma volume, it in turn is filtered by the kidneys. Thus, there is a complex, one-way, and tightly regulated circulation of CSF from the choroid plexus within the ventricles, through some narrow interventricular passageways (foramina or aqueducts), over the surface of the brain, and into the bloodstream. A variety of pathologic processes can disturb this delicate circulatory pathway, resulting in a relative or absolute imbalance between the amount of

fluid produced and reabsorbed. Some of these pathologic processes are congenital (e.g., congenital obliteration or stenosis of aqueducts or obliteration of the resorbtive capacity of the arachnoid granulations), while others are acquired (e.g., infections, intracranial hemorrhage, or residual hemorrhage from trauma or tumors). The resulting imbalance leads to a relative accumulation of cerebrospinal fluid within the ventricles of the brain that is called hydrocephalus.

Hydrocephalus

Hydrocephalus (sometimes referred to as "water on the brain") is a condition in which an excess of cerebrospinal fluid accumulates in the brain. In most cases, this is associated with an increase in the CSF pressure, which can be measured by placing a fluid filled catheter in the ventricle and connecting it to a manometer or strain gauge. CSF pressure is most commonly measured in centimeters of water rather than millimeters of mercury because manometric readings utilize the CSF itself for measurement and CSF has the same density as water. As the normal CSF pressure changes with age, the definition of "high" pressure varies with age as well. The normal pressure in an adult is thought to be less than 20 cm of water. However, a pressure of 15 cm of water in a normal adult may be abnormally high in an infant.

There are less common circumstances when the measured CSF pressure in the ventricle may be in the normal range. For example, ventricular enlargement associated with excess CSF volume causes brain dysfunction ("normal pressure hydrocephalus"). This condition is typically observed in elderly adults. Their scans do not show loss of brain surface volume, and they may be successfully treated with CSF shunts. A full discussion is beyond the scope of this paper, however.

Hydrocephalus must be distinguished from ventricular enlargement caused by loss of brain volume (sometimes called "hydrocephalus ex vacuo"), which may result from an acute or chronic injury to the brain. In the latter situation, the ventricular cavities are enlarged, CSF pressure is normal, but, unlike those with normal pressure hydrocephalus, MRI or PT scans show loss of brain volume. It is the generalized loss of brain substance (which causes the ventricular enlargement) that reflects the underlying brain disorder that is responsible for their brain dysfunction. CSF shunts do not help this condition.

Classification Systems

Hydrocephalus may be classified by the location of the primary CSF space enlargement. "External" hydrocephalus occurs when the subarach-

noid space surrounding the brain is enlarged. The ventricles may be modestly to moderately enlarged or rounded, but the intracranial pressure is normal. This condition may also be known as benign macrocrania of infancy or benign extraventricular hydrocephalus (BEH). Ventricular shunts are not used to treat external hydrocephalus. The more common and more serious "internal hydrocephalus" is notable for ventricular enlargement and elevation of intracranial pressure and is usually treated by implanting a ventricular shunt.

A further classification of internal hydrocephalus is that of "obstructive" versus "communicating." In the former, the CSF formed inside the ventricles cannot flow through its normal pathways (i.e., is obstructed) from reaching the absorbtive arachnoid villi along the sagittal sinus. Common sites of obstruction are the cerebral aqueduct (which connects the third and fourth ventricles) and the outlets of the fourth ventricle. Less commonly obstruction may occur at the foramen of Monroe or within the ventricles. Any diffuse injury (e.g., infection, hemorrhage, or trauma) in the brain has the possibility of eliciting scarring and inflammation that may contribute to the obstruction.

Another classification is based on etiology, but this is generally used in conjunction with the above classification scheme. This classification system defines broad classes of insult to the brain that resulted in the hydrocephalus. Examples include congenital, post-infectious, post-hemorrhagic, and post-traumatic7 hydrocephalus.

Diagnosis of Hydrocephalus

Hydrocephalus is typically suspected because of age-dependent signs of increasing intracranial pressure. In infants, this manifests as head growth that exceeds the normal rate, bulging of the normally flat anterior fontanelle (soft spot) of the skull, and behavioral signs, including irritability and unexplained vomiting. In its later stages, there can be continuous downward gaze of the eyes ("sun setting") and lethargy.

Older children and adults will complain of headache, nausea, and vomiting. Because the head cannot grow to accommodate significant increases in CSF volume after the age of 2 or 3 years, older children and adults are at increased risk for significant elevations of intracranial pressure (ICP). As such, hydrocephalus may cause double vision, papilledema (swelling of the optic nerve that can be seen by eye examination with an ophthalmoscope), confusion, and lethargy. Left untreated, this can progress to coma and death.

To diagnose hydrocephalus, doctors examine an image of the brain, using either CT or magnetic resonance imaging. CT provides excellent definition of the ventricles and is sufficiently rapid that sedation is rarely

necessary even in young children. As such, CT imaging has traditionally occupied the cornerstone of radiographic assessment of the child with hydrocephalus. Figure E.3 compares the CT scans of two children. The first scan reveals distention of the ventricles in a child with hydrocephalus. The second scan, from a different child, reveals transependymal flow at the tips of the lateral ventricles. This darker color within the brain substance at the tips of the ventricles is thought to result from fluid within the substance of the brain. Whether the fluid is egressing through the tissue from the distended ventricles or failing to gain access to the ventricles from the tissue remains an issue of controversy.

MRI provides images in multiple planes (axial, coronal, and sagittal) and provides better tissue definition. As such, MRI may provide important additional information that may elucidate etiology and facilitate classification and treatment. Figure E.4 is a sequence of MRI images of a child with hydrocephalus secondary to an intracranial tumor (which is not evident in these images). In this sequence, the left image shows the rounded, full appearing ventricles in the coronal plane. The image on the right shows ventricular distention and transependymal flow, which is evident as the darkened areas in the tissue at the tips of the ventricles in an image taken in the axial plane.

Prognosis

The contemporary prognosis for hydrocephalus is largely dependent upon the degree to which it is recognized and successfully treated and followed. The natural history of untreated hydrocephalus is ominous. While some patients are able to arrive at an equilibrium in which excess CSF volume is compensated by head growth and brain volume reduction to result in normal intracranial pressure, most are not. Even those that reach a compensated equilibrium often suffer cognitive and physical impairments related to the effects of adjusting to chronically increased pressure on brain development. Prior to the development of effective shunt systems, the natural history of most infants with hydrocephalus was that of progressive neurologic decline, macrocephaly (potentially grossly dysmorphic), and early death.

TREATMENT AND COMPLICATIONS

Treatment

The treatment of hydrocephalus is surgical. Although some medications have been shown to reduce the rate of CSF formation (acetazolamide, digoxin, and furosemide are the most common), they rarely are sufficient to relieve the symptoms of significant hydrocephalus. It is unusual to significantly delay

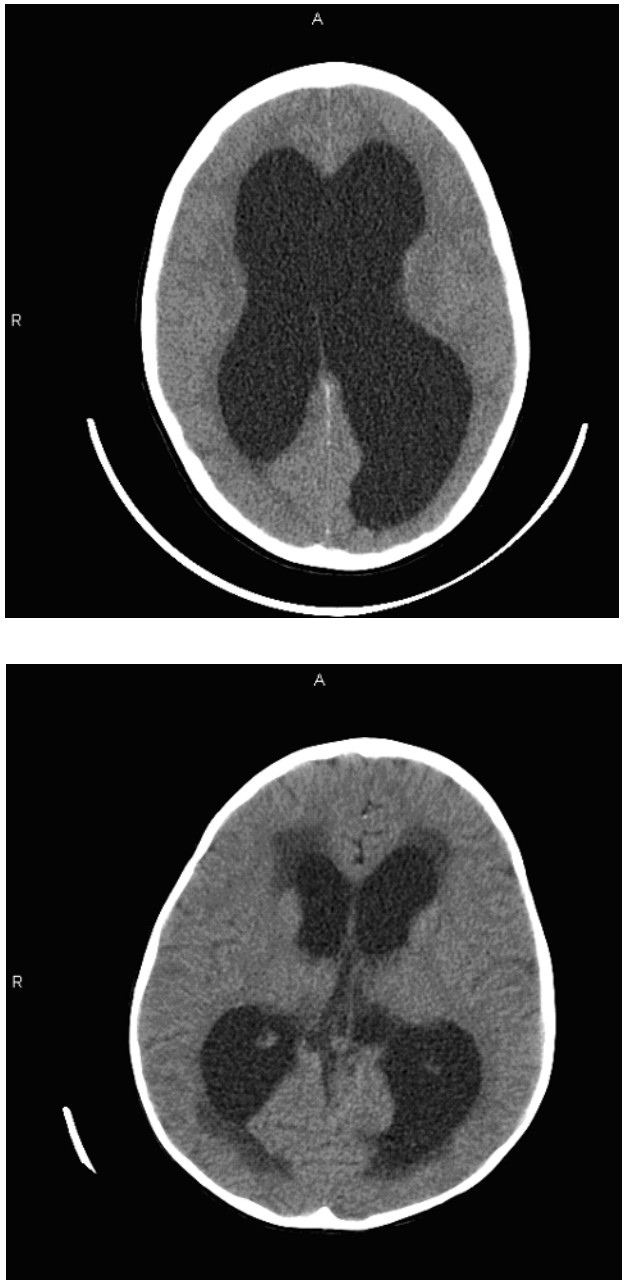


FIGURE E.3 CT scans of a child with hydrocephalus and a child with transependymal flow at the tips of the lateral ventricles. (Courtesy of Jeffrey P. Blount, M.D.)

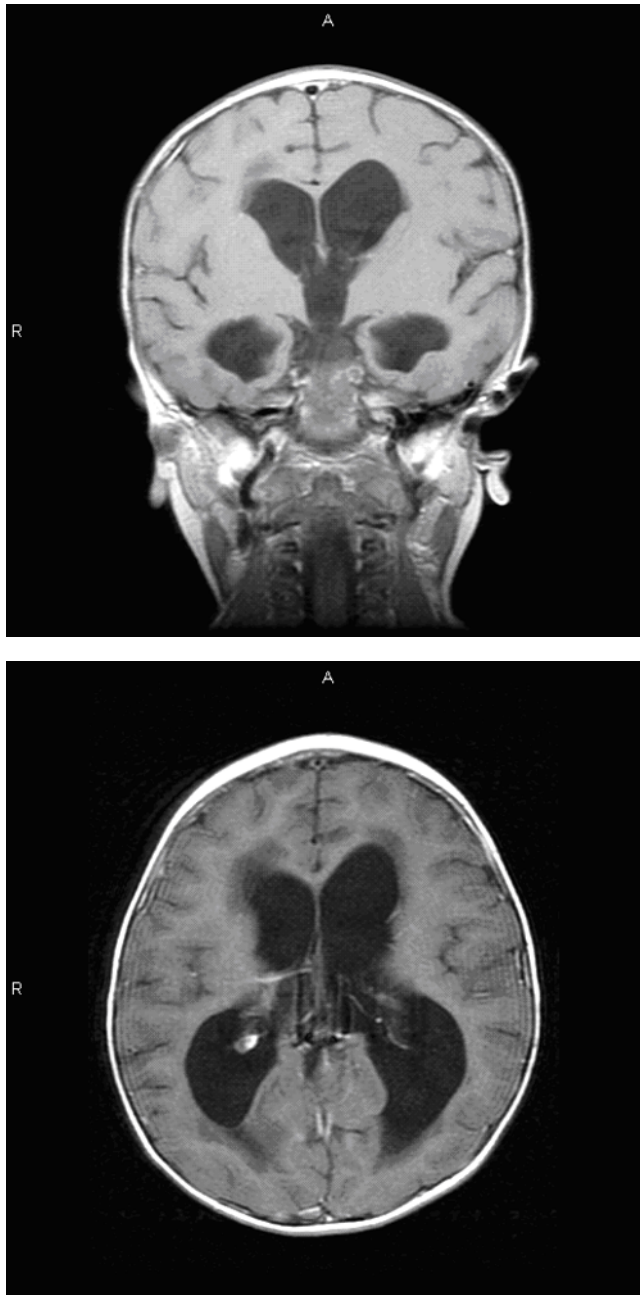


FIGURE E.4 MRIs of a child with hydrocephalus. (Courtesy of Jeffrey P. Blount, M.D.)

surgical treatment once the diagnosis is established. Occasionally these medications can be used to temporize until surgical therapy is undertaken, but there is no significant role for medical therapy in the long-term, contemporary treatment of hydrocephalus.

Historically, three conceptual surgical approaches have been undertaken to treat hydrocephalus: reduction of the rate of formation of CSF by ablation of the choroid plexus, establishment of alternative pathways for the spinal fluid to reach the arachnoid granulations, and shunting of the fluid to a body cavity where it can be absorbed (5).

Prior to the development of valve-regulated CSF shunts, attempts were made to decrease the formation of CSF by surgical removal of the choroid plexus (choroid plexectomy). This intervention was developed because the choroid plexus was the site where CSF was known to be generated. Later, it became evident that CSF also egresses directly from the brain tissue itself. While occasionally successful in establishing a "compensated" state, choroid plexectomy was rarely curative and has been relegated to be of only historic interest with an important exception. Choroid plexectomy may be highly useful in treating hydranencephaly—intrauterine destruction of the brain caused from infections or infarcts, which results in loss of the cortex and replacement with CSF.

A number of surgical interventions have been proposed to bypass the site of obstruction to CSF flow surgically. The first historical efforts attempted wholly intracranial diversion from the trapped ventricles. One such procedure (popularized by Torkildsen during the early 1950s) involves placement of a valveless tube from the ventricle to the subarachnoid space (usually the cisterna magna at the base of the skull). Despite initial claims of success, ventriculocisternal diversion did not provide long-term control for hydrocephalus and is no longer used.

Another approach involved the surgical creation of an alternative pathway past an obstruction to the subarachnoid space and arachnoid granulations. Anatomically, the most inviting location to pursue this was through the floor of the third ventricle. Hydrocephalus causes distention of the third ventricle with thinning of the floor so that an opening can be made to the subarachnoid space (third ventriculostomy) without disturbing any functional neurological tissue. When done as a major operation involving widely opening the skull (craniotomy), it had significant risk of death and disability. In the 1950s and 1960s, emerging capabilities in stereotactic neurosurgery allowed the procedure to be performed with less morbidity than with open approaches. However, the puncture was made without direct visualization or x-ray guidance and severe complications occurred.

In the late twentieth century, advances in endoscopy led to a resurgence of interest in third ventriculostomy. Contemporary endoscopes allow excellent visualization of the floor of the third ventricle. Endoscopic third ven-

triculostomy is an important procedure in contemporary management of hydrocephalus, but it is an effective intervention only for a subset of patients with hydrocephalus. Long-term results of and patient selection for endoscopic third ventriculostomy remain topics of considerable interest and continued investigation (6).

Valve-Regulated CSF Shunts

The first reliable valve-regulated CSF shunt was developed in the 1950s by John Holter after his son was born with spina bifida and hydrocephalus. Holter was a machinist and, faced with a condition for which no reliable treatment was available, designed and produced the Holter valve in conjunction with neurosurgeon Eugene Spitz. This valve was rapidly adopted and represented a major breakthrough in the treatment of hydrocephalus. Other differential pressure valves were subsequently developed, and major and minor modifications of devices and techniques followed (2).

Like all shunts the initial shunt consisted of a ventricular catheter, a valve, and a distal catheter. The *ventricular catheter* is the portion of the shunt that penetrates the skull and the brain tissue. The *valve* prevents overdrainage of cerebrospinal fluid. In the absence of a valve, fluid can rapidly drain down the tube and cause acute drops in the intracranial pressure. Acutely this causes severe headaches, vomiting, and lethargy and may contribute to the collapse of the ventricles. Subsequently, ventricular collapse may cause the surface of the brain to pull away from the inner surface of the skull. This can result in the disruption of draining veins and the accumulation of potentially life-threatening subdural hematomas. The *distal catheter* is the portion of the shunt that drains the CSF from the valve to its ultimate body cavity for absorption. The most popular location for the distal drainage catheter in early shunts was the right atrium of the heart. The catheter was usually inserted through the jugular vein, requiring sacrifice of the vein or one of its major tributaries. In some cases, it was even placed directly in the atrium by an operation through the chest.

With time and experience, a number of complications related to the placement of CSF shunt catheters within the vascular system were identified. When such catheters stopped working, the revision operation could be quite challenging (7). In 1968, a study concluded that the relative position of the catheter in the superior vena cava was critical to its continued function: the rate of malfunction rose rapidly as the catheter rose from the level of the sixth to the fourth thoracic vertebra as visualized on a chest x-ray. Routine revisions were recommended to prevent such malfunctions (8). Although this observation identified that shunt failure was common in infants in the first 36 months after placement, it took the authors 11 years to accumulate and publish that experience. Another method for predicting

the need for elective lengthening of the atrial catheter was reported in 1976 (9). Other sites for the distal catheter were explored, before and after the introduction of the Holter valve, including the mastoid (10), sagittal sinus (11), gall bladder (12), and pleural (13) and peritoneal (14) cavities. Because of the ease of revision and less serious cardiovascular and infectious complications of the ventriculo-peritoneal shunt, it became the most popular site for catheter implantation to date, with atrial and pleural shunts a distant second and third in frequency of utilization (15).

Complications Drive the Development of the Modern CSF Shunt

The most common problems with valve-regulated shunts are obstruction and infection (16), (17), (18). The youngest patients seem at highest risk of shunt failure (19), (20). Obstruction may occur in any part of the system (ventricular catheter, valve, or distal catheter) (2), but the most common site is the ventricular catheter. Figure E.5 shows an endoscopic view of a ventricular catheter partially covered in fibrinous debris. Strands of debris can be seen to be gradually occluding one of the holes of this ventricular catheter. Gradual occlusion of the ventricular catheter by similar tissue is thought to be the most common cause of VP shunt malfunction. Other causes of malfunction include discontinuity of the system (disconnec-

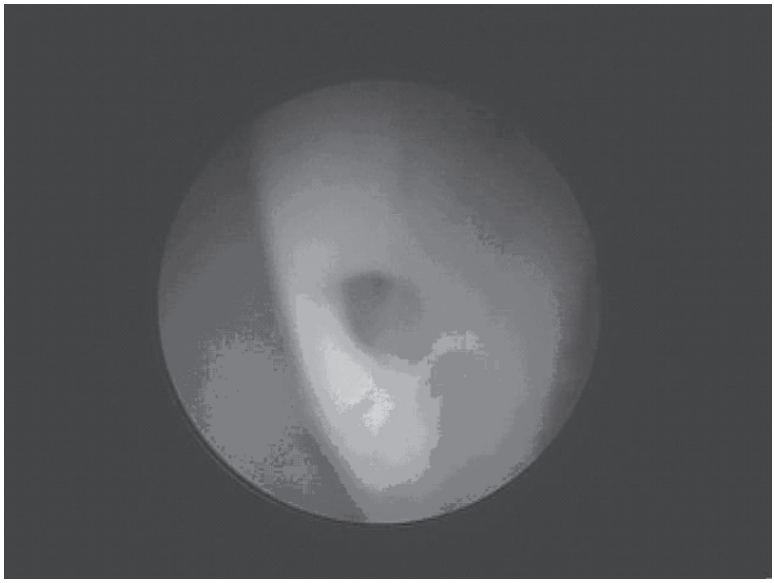


FIGURE E.5 Endoscopic view of a ventricular catheter partially covered in fibrinous debris. (Courtesy of Jeffrey P. Blount, M.D.)

tion or fracture of tubing), migration of the system (often, but not always, associated with disconnection or fracture), perforation of an organ at the site of the distal catheter, or development of a cyst around the end of the distal catheter (particularly related to shunts with distal catheters in the peritoneum).

To decrease the number of shunt obstructions, a number of technical innovations focused on the ventricular catheter. It is hypothesized that ingrowth of choroid plexus tissue into the small proximal holes of the ventricular catheter was the mechanism by which ventricular catheter obstruction occurs. Consequently, several catheters were developed that attempted to prevent ingrowth of choroid plexus. The most popular was the flanged catheter that featured soft silastic flanges at the most distal end of the ventricular catheter. In theory, the flanges were to keep choroid away from the holes in the ventricular catheter. Unfortunately, in clinical practice they were found to be optimal sites for choroid plexus adherence. This adherence made necessary shunt revisions difficult. The flanges increased the surface area of the device, which, in turn, increased the frequency of intraventricular hemorrhage from avulsion of the choroid plexus.

The number and size of the holes in the proximal part of the ventricular catheter have also been modified in an ongoing effort to reduce the rate of ventricular catheter failure. No significant improvement in overall ventricular catheter longevity has been realized despite differences in size, number, and positioning of holes in the proximal catheter.

Another recent technical innovation involving the ventricular catheter is the impregnation of the catheter with antimicrobial agents. This is discussed further in the section on shunt infection.

Valve design has similarly undergone extensive, continuous technical revisions and innovations. The earliest prototype of the Holter valve featured two rubber condoms with slits at either end of a piece of tubing. Other early valves featured simple differential pressure mechanisms that allowed flow when pressure in the proximal part of the shunt reached a given value. These valves prevented continuous drainage but did little to prevent siphoning or over-drainage. To improve valve function, the valve was moved to the distal end of the shunt. The distal slit valve included a tiny slit in the distal end of the peritoneal catheter, which provided sufficient resistance to CSF outflow to function meaningfully as a valve. The Raimondi distal spring valve (a peritoneal valve) was less successful. This valve featured a spring-like device in the distal end of the peritoneal catheter that functioned to resist CSF outflow. Unfortunately, the spring provided sufficient rigidity that hollow viscus perforation was a frequent and serious problem. Concern over this event led a small group of pediatric neurosurgeons to take the unprecedented step of writing to the FDA in 1978 to petition for the removal of the device. As a result of this action and

word-of-mouth dissemination of the knowledge of bowel perforation complications, the distal spring valve fell quickly out of use.

Advances in the understanding of CSF physiology fostered technologic advances in valve design in the 1980s and early 1990s. Prior to this, all shunt valves functioned through differential pressure. The next sequence of valve design added flow control to differential pressure. Several valves were marketed that incorporated these concepts (e.g., Orbis-Sigma 1, Delta valve).

Another recent innovation in shunt valve design was the introduction of valves that can be externally adjusted to change the pressure setting of the valve, allowing the performance characteristics of the valve to be changed without requiring surgical replacement (21). These valves were used to treat some forms of slit ventricle syndrome, to allow for changes in normal intracranial pressure with growth from infancy to adolescence, and to prevent subdural hemorrhage consequent to shunt over-drainage. Overall effectiveness for each indication remains to be definitively demonstrated.

The shunt design, marketing, and pediatric neurosurgery communities hoped that such advancements, based on improved understanding of CSF physiology, would predictably result in real and demonstrable improvements in shunt longevity (22). Unfortunately, as documented in the multicentered prospective shunt design trial, these aspirations were not realized, and rates of shunt failure remained relatively unchanged (23), (24).

Infection

Infectious complications have plagued shunts since they first were implanted (25), (26), (27), (28). Infection is an important problem for two main reasons. First, shunt infections are associated with significant morbidity, mortality, and expense. Second, shunt infections are largely iatrogenic events that have proven markedly resistant to extensive efforts aimed at reducing or eliminating them (26), (28), (30), (31). Shunt infection may result in ventriculitis, which is similar to meningitis except that it is centered within the ventricles of the brain rather than diffusely throughout the subarachnoid space. The infection itself may injure the brain and result in developmental delay, direct neurologic deficits, or seizures. The patient's immune response to the infection may be similarly damaging to the brain and worsen the injury and resulting deficit. The infection may cause obstruction of the shunt with secondary elevation of intracranial pressure and risk for cerebral herniation. If undetected, shunt infections may progress to severe neurologic injury or death (32), (33).

Treatment is invasive and expensive. Infection occurs at a rate of 7–10 percent of operations (34). Surgical shunt removal with implantation of a temporary drain and intravenous antibiotics are the cornerstone of care

(35). Once the infection is cleared, a second operation is needed to insert a new shunt. A recent estimate suggested that treatment of an individual shunt infection costs in excess of $50,000 (36). Overall risks of shunt failure and infection correlate with clinical experience of the institution where implantation is performed (37). In-hospital mortality varies by surgeon and hospital experience, ranging from 0.1 percent to 0.8 percent of hospital admissions (38).

The most common microorganisms to cause shunt infections are *Staphylococci* from the skin. Other cutaneous bacteria are frequently implicated, and enteral organisms (from the gut) may rarely be implicated. The preponderance of cutaneous organisms is strongly suggestive that the critical event in the pathophysiology of shunt infections is inoculation of the shunt with skin bacteria at the time of shunt insertion. A wide variety of interventions have been proposed to reduce the risk of shunt infection. The only intervention that has been proven to reduce the rate of infection is the provision of intravenous antibiotics prior to the initiation of shunt surgery (39). Clinical studies also indicate that a dedicated program toward reducing shunt infection often results in reductions of shunt infection rate. In poorly controlled, retrospective reviews, individual centers have reported utilization of protocols that resulted in lower shunt infection rates. However, no single technique or procedure has significantly reduced infection rates across time and multiple clinical centers (40), (41), (42). The number of properly controlled, prospective trials is very limited (43).

The manifestation of the shunt infection is dependent upon the anatomic location of the shunt. Early CSF shunt systems employed the atrium for the distal catheter placement. As such, blood and heart valve infections were frequent. Many of these infections were not easy to diagnose. In fact, catheters can be colonized by staphylococcus aureus without causing overt infectious signs in the shunted child. However, chronic exposure to the organism could lead to immune-complex glomerulonephritis (an inflammatory kidney disease) that might result in kidney failure (44). This condition is called "shunt nephritis" (45), (46). Shunt infection investigators were intrigued by shunt nephritis through the 1970s, but as the peritoneal shunt became more popular, other issues in shunt infection dominated publications (Figure E.6).

One of the principal advantages in utilizing the peritoneum for distal catheter placement is the relatively minor damage imparted by a shunt infection (47), (48), (49). The peritoneum has a well-recognized capability to seal-off/wall-off localized infections. Continued CSF accumulation within the loculated peritoneum can result in a localized collection of infected CSF called a pseudocyst (50). The severity of infection-related complications is significantly less for peritoneal shunts, and the recognition of this and the

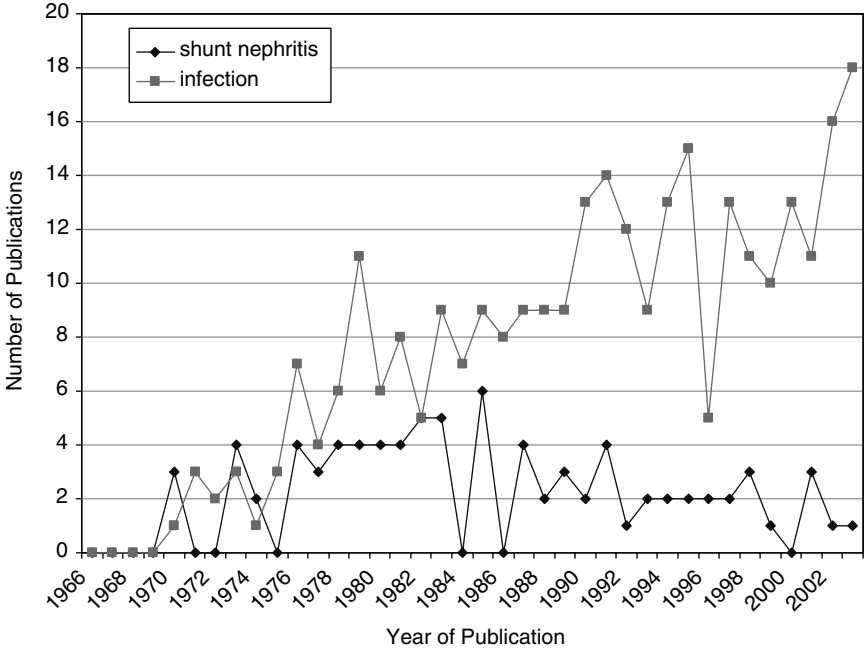


FIGURE E.6 Shunt infection publications by year.

gradual increase in the number of peritoneal shunts represents a successful hallmark in the history of CSF shunts.

The focus on infection and the inability to eliminate it as an important complication have led recently to the introduction of shunt components, such as ventricular and distal catheters, impregnated with antibiotics (51). Several prototypes are currently available and preliminary reports suggest their potential effectiveness (52).

Other Complications

A host of other complications has been described. All have important implications for shunted patients and the health care system. Because the shunt is an implant, its repair requires an operation. Virtually all infections require that the infected shunt be removed and replaced. Obstruction, disconnections, fractures, and migrations all require surgical correction. Organ perforation may require shunt repair or replacement in addition to surgical intervention. Hemorrhage can sometimes cause additional brain

damage. The spread of a brain tumor outside of the central nervous system through a shunt can seriously complicate the treatment of the tumor. Heart, lung, and kidney failure, which can result from shunt infection or malfunction, can be life-threatening.

Reports of Complications

To examine the identification and attempts to devise ways of treating and preventing complications, we performed a search of the MEDLINE and OLDMEDLINE databases with the following strategy:

1	Exp HYDROCEPHALUS/co and exp HYDROCEPHALUS/su [Complications, Surgery]	560
2	exp Cerebrospinal Fluid Shunts/ae, mo [Adverse Effects, Mortality]	1,713
3	1 or 2	2,184

The 2,184 articles identified were then screened by title and abstract (where necessary) to identify those that dealt directly with complications of CSF shunts. A category of "general" was identified for comprehensive reviews of CSF shunts that might contain discussions of complications. This category of publication was used primarily in the early days of shunt experience. Only 13 of the 128 articles in this category were published after 1976.

The articles discussing complications were grouped according to type of complication. The large category of "malfunction" includes general studies of malfunction and specific studies of occlusion, disconnection (including fracture of the catheter), migration (of a portion of the system away from its site of implantation), and perforation of an organ by the distal catheter of the shunt system.

The large category of infection includes general studies of shunt malfunction and specific studies of shunt nephritis, infected abdominal cysts, or peritonitis.

Other identifiable categories of complication include uninfected abdominal cysts, intracranial hemorrhage caused by the shunt, tumor metastases through the shunt, pneumocephalus (symptomatic air in the head related to the shunt), slit ventricles (ventricles that become smaller than normal after shunting and are associated with symptoms), cardiopulmonary (including heart failure, pulmonary embolism, lung dysfunction, or catheters that perforate the heart or become loose in the vascular system), and death. Articles describing other complications or studying multiple types of complications were classified as "miscellaneous." Table E.1 shows the distribution of the 1,272 articles. (The entire reference list is available upon request.)

TABLE E.1 Articles on Shunt Complications by Type of Complication

Complication		Articles	
		#	%
Malfunction		179	14.1
	Occlusion	59	4.6
	Disconnection	16	1.3
	Migration	29	2.3
	Organ perforation	75	5.9
Infection		388	30.5
	Infection	293	23.0
	Abdominal: cyst or peritonitis	7	0.6
	Shunt nephritis	88	6.9
Abdominal Cyst	(no infection)	43	3.4
Hemorrhage		55	4.3
Abdominal	metastasis	54	4.3
Pneumocephalus		28	2.3
Slit ventricles		33	2.6
Cardio-pulmonary		68	5.3
Mortality		12	0.9
Miscellaneous		412	32.4
Total		1,272	

The relative frequency of publication of types of complication by year is shown in Figure E.7. The early dominance of cardio-pulmonary complication reports is replaced by dominance of infection reports after 1976 and is explained by the evolving predominance of ventriculo-peritoneal shunts.

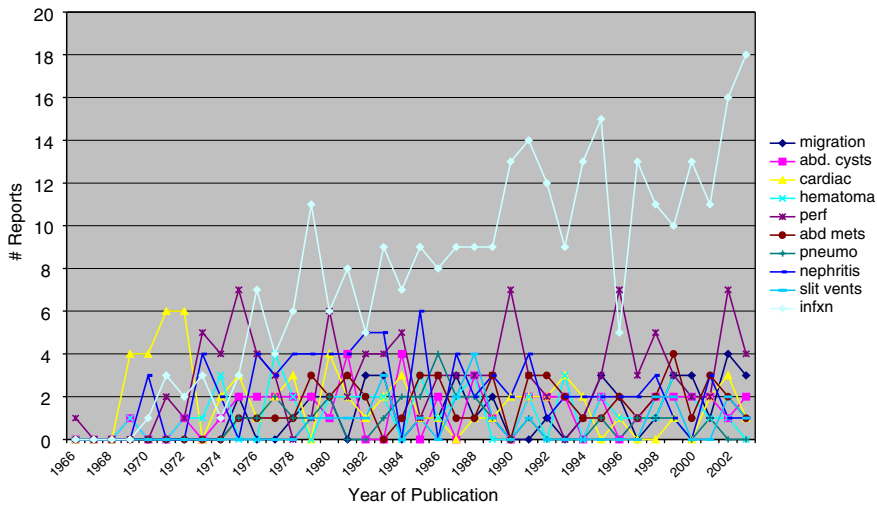


FIGURE E.7 Literature reports of shunt complications.

A cursory review indicates that CSF shunts have many different serious complications, including death, which may result from unrecognized or untreated malfunction and infection as well as a host of less common situations.

Issues of Growth and Active Lifestyle

Three specific issues related to growth and lifestyle has been overtly addressed by shunt investigators. The first is the need to revise atrial catheters placed in young children, discussed above. The second is the development of a strategy to avoid revision of peritoneal catheters because of growth. The third is the fracture of catheters under the skin as they cross from the neck to the chest.

Early in the experience with peritoneal catheters, some were concerned that excessive catheter length might be problematic (perhaps wrapping around the bowel and leading to bowel obstruction or causing discomfort because of amount of foreign material) and used catheters just long enough to enter the peritoneal cavity at the time of placement. Children could outgrow these catheters, requiring surgical revision to lengthen the peritoneal end. A catheter that would expand with growth was reported in 1975, but did not achieve widespread acceptance (53). Another theory suggested that a specific, optimal length of catheter could be determined for each patient, avoiding a presumed problem related to excessive catheter length (54). This approach likewise failed to achieve currency. A number of reports have suggested ways to add length to existing catheters (55), (56), (57). Over time, it became common practice to insert catheters long enough to allow for growth through maturity and to avoid elective operations that lengthened the tubing. Recently, this practice has been validated in the published literature (58). Because of the content and nature of the FDA reporting process, these problems are not identified in the formal postmarket surveillance process.

Finally, the issue of fractures of the distal catheter in the neck has been investigated (59), (60), (61). Although it has not been possible to definitively prove that these fractures are related to activity, this is hypothesized to be an important factor because of the consistent location of the fractures.

THE PERIOD OF REGULATION

Regulation Prior to Marketing

In 1976, amendments to the Federal Food, Drug, and Cosmetic Act gave the FDA its first real authority to regulate medical devices. Devices were placed in three classes. Class I devices "present minimal potential for harm to the user" and are the subject of the least regulatory control. Class II

devices "are those for which general controls alone are insufficient to assure safety and effectiveness, and existing methods are available to provide such assurances." These devices are subject to special controls, such as special labeling or performance standards. For a Class II device that is used in supporting or sustaining human life, FDA must identify special controls that will provide adequate assurance of safety and effectiveness. Class III devices "are usually those that support or sustain human life, are of substantial importance in preventing impairment of human health, or which present a potential, unreasonable risk of illness or injury" Class III devices are subject to the most stringent regulation (62).

Although CSF shunts are necessary to sustain life in many patients with hydrocephalus and their failure can lead to death unless properly detected and treated, CSF shunt systems have been classified as Class II in the Code of Federal Regulations (21 CFR 882.5550) (63). In 1999, the Systemic Technology Assessment of Medical Products (STAMP) Conference (sponsored by the FDA) investigated the topic of CFS shunt technology. The introduction to the subsequent report indicates that the decision to classify shunts as Class II medical devices was "based upon the belief that standards could be written to assure the safety and effectiveness of marketed shunts, and that clinical experience had proven shunts to be reasonably safe and effective" (64).

The rationale expressed in the initial classification is similar to the rationale described above and, in addition, states that the panel responsible for the classification believed that "the characteristics of central nervous system fluid shunts and their components are reasonably well established." It further stated that "the complications associated with these devices have been extensively reported in the literature," and it acknowledged a mortality rate in patients treated with shunts of 5–35 percent. The panel noted that the device was primarily used in children. The Commissioner of FDA further commented that he doubted "that requirement [sic] premarket approval of these devices will improve the complication rate associated with their use" (43 FR 55714-55716, 1978).

Class II devices do not generally require "premarket approval" (PMA), but premarketing notification (510[k] notification) must be submitted to and cleared by FDA. This gives FDA the opportunity to assure that general controls and specific controls for the device are met. In FDA terminology, these devices receive clearance rather than approval. Applicants for clearance usually must show that the devices meet technical standards for biocompatibility, function, and reliability through bench testing. They must also demonstrate the device to be "substantially equivalent" to a device that was either marketed before May 28, 1976, or has been shown (through the notification or clearance process) to be substantially equivalent to such a device. Current, relevant technical standards are embodied in the Interna-

tional Organization for Standardization (ISO 7197:1997) and American Society for Testing and Materials (ASTM F647-94[2000]) documents.

The FDA maintains a public, searchable database of releasable decisions on 510(k) applications cleared after January 1999 (65). Table E.2 includes 26 codes that the FDA may use to describe its determinations about whether a device meets the criterion of substantial equivalence. The actual, online database, however, only includes decisions for devices that are found to be substantially equivalent. Those familiar with FDA confidentiality, trade secret, and privacy regulations might expect this, given the prominent use of "releasable" in the description of the database. Less expert users of the database might, however, expect to find negative decisions,

TABLE E.2 Codes for Determination of Substantial Equivalence by FDA for 510(k) Notifications

Code	Description
Determination of Substantial Equivalence listed in 510(k) database	
AN	Approved Evaluation of Automatic Class III Designation
ST	Substantially Equivalent – Subject to Tracking Regulations
PT	Substantially Equivalent – Subject to Tracking and Postmarket Surveillance
SF	Substantially Equivalent – Waiting on Future Policies
SS	Substantially Equivalent – Special Labeling
SE	Substantially Equivalent
SA	Substantially Equivalent – Awaiting Device Approval
SW	Substantially Equivalent – Awaiting Drug Approval
CS	Substantially Equivalent – CLIA Submission
SK	Substantially Equivalent – Kit
KD	Substantially Equivalent – Kit with Drugs
SI	Substantially Equivalent – Market after Inspection
SP	Substantially Equivalent – Postmarket Surveillance
PR	Substantially Equivalent – Proposed Recision
SU	Substantially Equivalent – with Limitations
SN	Substantially Equivalent – for Some Indications
SD	Substantially Equivalent – with Drug
Determination of Non-Substantial Equivalence listed in FDA decision codes	
FB	Subject to 515(b) – Requires PMA
NE	Not Substantially Equivalent
SC	Not Substantially Equivalent – Cannot Market
SL	Not Substantially Equivalent – Improper Label
RE	Rescind Substantial Equivalence
UD	Unable to Determine Equivalence
UO	Unable to Determine Equivalence – Outstanding Drug Issue
UR	Not Substantially Equivalent – Unreliable Data
OD	Unable to Determine Equivalence – Outstanding Device Issue

SOURCE: (65), (66).

especially because the documentation for the database defines nine codes for various kinds of negative decisions.

A search of the 510(k) database through January 2005 (65) produced 166 records for code JXG (shunts, central nervous system), 8 records for HCA (catheter, ventricular), and 1 record for NHC (catheter, ventricular [containing antibiotic or antimicrobial agents]). HCD (cannula, ventricular) and GYK (instrument, shunt system implantation) were not included in further searches as these devices are not permanently implanted shunts. All 175 devices were cleared as substantially equivalent (SE). According to this database, the FDA has never required postmarket surveillance, tracking, special labeling, or placed limitations beyond those proposed by the manufacturer for CSF shunts.

The search also identified a valve system that is electromagnetically adjustable to 17 different pressure settings (67). All previously marketed shunts operated at a single, predetermined pressure. These pressure settings are susceptible to alteration by strong magnetic fields, such as magnetic resonance imaging scanners. Although not required by the FDA, this submission included a randomized clinical trial, comparing the programmable shunt to its non-programmable predecessor (21). To date, the FDA has not required a premarket approval application for any CSF shunt.

Based in part on the descriptions provided above, it is clear that the CSF shunt is considered to be a mature device from a regulatory point of view. Despite its use to "support or sustain human life" and its "substantial importance in preventing impairment of human health," FDA does not require the intense scrutiny applied to Class III life-saving devices introduced into clinical practice after 1976. One must ask if this is a reasonable conclusion or if this conclusion is based on short-term effectiveness without sufficient consideration of long-term effectiveness and complications.

Postmarketing Surveillance

In 1999, the FDA convened the previously mentioned STAMP conference, "Shunt Technology: Challenges and Emerging Directions." The conference reviewed "families of closely related medical devices having broad use and most often, several years of marketing experience, as well as, a significant potential for adverse events." In presentations, patient advocates, industry representatives, and physicians familiar with cerebrospinal fluid shunts and the associated complications stressed continuing difficulty with problems of shunt function and infection. The report states that "over 60% of shunt patients manifest some type of shunt complication over their lifetime such as shunt obstruction, over-drainage, infection, device migration, disconnection and fracture." The report summary mentions the possible development of patient information cards and online databases that

would allow more comprehensive collection of information on shunt complications using standard definitions, but makes no specific recommendations (64).

It is clear that the approved CSF shunt devices continue to have important problems with both function and infection. The existing system for monitoring these devices for problems should be examined for effectiveness both in identifying problems and in prompting corrective action.

The 1976 Medical Device Amendments granted FDA authority to issue regulations requiring adverse event reporting for marketed medical devices. FDA issued these medical device reporting regulations in 1984. A medical device reportable event as defined by the statute means:

> (1) An event about which user facilities become aware of information that reasonably suggests that a device has or may have caused or contributed to a death or serious injury; or (2) An event about which manufacturers or importers have received or become aware of information that reasonably suggests that one of their marketed devices:
> (i) May have caused or contributed to a death or serious injury; or
> (ii) Has malfunctioned and that the device or a similar device marketed by the manufacturer or importer would be likely to cause or contribute to a death or serious injury if the malfunction were to recur. (21 CFR 803.3)

Subsequent adverse event reports were collected in the Medical Device Reports (MDR) database. To strengthen the reporting system, Congress enacted the Safe Medical Devices Act of 1990 (SMDA), which established requirements for reporting by device manufacturers, distributors, and user facilities. The FDA established a new database, Manufacturer and User Facility Device Experience (MAUDE), and began the transition from the MDR database in 1992. Since August 1996, MAUDE has been the exclusive adverse event report database.

In 1990, Congress also enacted separate regulatory authority for postmarket surveillance. The FDA website provides the following statement regarding the purpose of postmarket surveillance (68).

> The primary objective of postmarket surveillance is to study the performance of the device after marketing as it is to be used in the general population for which it is intended. Generally, the primary variables to be studied are morbidity or mortality. The major interest lies in device failure and its attendant impact on the patient.
>
> Postmarket surveillance is considered a warning system for the early detection of potential problems within a reasonable time of their first marketing. The intent of the regulation is to:
>
> - Identify problems
> - Provide safety warnings

- Provide information not available from the medical device reporting regulation
- Provide actual use of safety and effectiveness information.

ECRI (formerly the Emergency Care Research Institute), a not-for-profit health services research agency, maintains a version of the MDR and MAUDE databases with additional search capabilities. Both versions of the databases were used for this report. Searches were performed in December 2004. The strategy summarized in Table E.3 was used to search the MDR database.

This search produced 1,762 reports relevant to CSF shunts submitted to the MDR database from 1978 through 1996. Because of misclassifications leading to the inclusion of non-shunt devices and overlapping product codes that include CSF devices that are not implanted shunts (e.g., external ventricular drains, CSF shunt programmers, and devices for passing shunt catheters subcutaneously), the records were reviewed by the author (SJH) to identify misclassifications and reports not related to implanted CSF shunts. The final result was 1,555 reports regarding implanted CSF shunts.

The MAUDE database was searched in June 2004 with the strategy ((((“CEREBROSPINAL FLUID” OR CSF OR VP OR V-P OR VA OR VENTR* OR HYDROCEPH* OR CNS OR CENTRAL) AND SHUNT) OR (“NEURO VALVE” OR PUDENZ OR “SHUNT KIT” OR “POSTERIOR FOSSA” OR OSV OR DELTA)))). This produced 2,985 records of reports submitted from 1992 through 2004. These were reviewed for accuracy and a number of misclassifications by FDA product code were identified. Thirty-four were clearly shunts misclassified as another device (Table E.4). Others were non-shunt devices misclassified with a shunt code. Cleaning of the list resulted in 2,298 records of reports to the MAUDE database regarding problems with CSF shunts. An amended search in December 2004 increased the number of reports to 2,472.

Classification of Complications

In Part 2, we presented a classification of complications based on review of the literature. Both the MDR and MAUDE reports list reporter-classified outcomes as: death, serious injury, malfunction, or other. Because the MDR database could only be obtained in a text file, the “EFFECT TYPE” was identified by text searching the 1,762 reports that were identified in line S9 of the search strategy in Table E.3. All effect types other than “DEATH,” “SERIOUS INJURY,” or “MALFUNCTION” are grouped as “OTHER.” The MAUDE database was available in spreadsheet format allowing a more detailed search. The responses “OTHER,” “NO

TABLE E.3 Search Strategy (MDR Reports) for Adverse Events for CSF Shunts

Step	Items	Description (use 4 digit years)
S1	56,618	SF=(AI OR ABS)
S2	1,508	SO=(HEALTH()DEVICES?)
S3	657	PC=(16-244?)
S4	486	S3 NOT S1
S5	826	PC=(10-704? OR 16-151? OR 10-769? OR 15-588? OR 16-244? OR 17-090? 04 17-734?)
S6	589	S5 NOT S1
S7	1,709	FP=(JXG? OR GYK? OR HCD? OR HCA?)
S8	1,709	S7 NOT S1
S9	1,762	S7 OR S6
S10	111	S9 AND (OCCLU? OR BLOCK? OR OBSTRUCT*)
S11	77	S9 AND (DISCONNECT? OR FRACTUR?)
S12	6	S9 AND MIGRAT?
S13	7	S9 AND (PERFORAT? OR EXTRU? OR PENETRAT?)
S14	49	S9 AND (INFECT? OR VENTRICULITIS? OR MENINGITIS?)
S15	1	S9 AND (PERITONITIS? OR PSEUDOCYST? OR PSEUDO (1N) CYST?)
S16	0	S9 AND CYST (3N) ABDOM?
S17	0	S9 AND CYST AND PERITON?
S18	0	S9 AND (NEPHRITIS OR GLOMERULONEPHRITIS)
S19	49	S9 AND (HEMORRHAG? OR HAEMORRHAG? OR HEMATOMA? OR HAEMATOMA? OR BLEED?)
S20	0	S9 AND METASTAS?
S21	1	S9 AND TUMOR? AND (ABDOM? OR PERITON?)
S22	22	S9 AND (AIR OR PNEUMOCEPHALUS)
S23	424	S9 AND (SLIT OR INTRACRANIAL()HYPOTENSION OR LOW()PRESSURE) OR OVERDRAIN? OR OVER()DRAIN?)
S24	30	S9 AND (HEART CARDIAC OR ATRI? OR SUPERIOR() VENA()CAVA OR SUPERIOR()VENACAVA OR ENDOCARDITIS OR VEGETATION)
S25	15	S9 AND ET=DEATH
S26	9	S9 AND DIED
S27	16	S25 OR S26
S28	388	S23 NOT (S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S19 OR S21 OR S22)
S29	295	(S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S19 OR S21 OR S22)NOT S28
S30	0	S29 AND (HAIR OR FAIR)
S31	24	S11 AND (HEART OR CARDIAC OR ATRI? OR SUPERIOR()VENA()CAVA OR SUPERIOR()VENACAVA OR ENDOCARDITIS OR VEGETATION)
S32	11	S11 AND ET=DEATH
S33	7	S11 AND DIED
S34	12	12 S32 OR S33
S35	0	S11 AND (BRAIN()DEATH OR BRAINDEATH OR BRAIN()DEAD OR BRAINDEAD)
S36	442	S11 AND (SLIT? OR INTRACRANIAL()HYPOTENSION OR LOW()PRESSURE OR OVERDRAIN? OR OVER()DRAIN?)
S37	36	S11 AND S19 OR S20 OR S21 OR S22 OR S23

TABLE E.4 CSF Shunt Reports in the MAUDE Database Misclassified as a Non-Shunt Device

Listed FDA Product Code	Actual Product	Report #
<blank>	Shunt catheter	36
	Shunt catheter	5,787
	VP shunt	9,189
	VP shunt	9,200
	VP shunt	9,201
	VP shunt	19,227
	VP shunt	20,112
KPM *(peritoneo-venous shunt)*	VP shunt	941
	VP shunt	16,815
FIQ *(cannula, A-V shunt)*	Shunt catheter	2,336
CAR *(monitor, spinal fluid pressure, electrically powered)*	Shunt catheter	5,860
LID *(not currently listed, "ventriculo-amniotic" in database)*	VP shunt	9,511
	VP shunt	15,964
	VP shunt	16,748
LXL *(not currently listed, "valve-shunt-fluid" in database)*	VP shunt	25,331
	VP shunt	28,084
	VP shunt	507,413
MAJ *(catheter, percutaneous, intraspinal, short-term)*	VP shunt	65,062
HCA *(catheter, ventricular)*	VP shunt	105,654
	VP shunt	174,723
	VP shunt	206,462
	VP shunt	210,976
	VP shunt	228,231
	VP shunt	238,155
	VP shunt	394,625
	VP shunt	437,978
	VP shunt	446,166
GBW *(catheter, peritoneal; General and Plastic Surgery)*	VP shunt	206,467
	VP shunt	220,542
	VP shunt	241,343
	VP shunt	241,350
	VP shunt	385,607
GWB *(antisera, fluorescent, all types, streptococcus pneumoniae) (probable typographical error)*	VP shunt	501,635
JQG *(radiometric, F259, iron-binding capacity)*	VP shunt	501,622
	VP shunt	501,934

ANSWER PROVIDED," and blank fields were grouped as "OTHER." The shunt reports classify as follows (Table E.5).

In the MDR database, the refined text search for "MORTALITY" (Table E.3, line S34 and 35) produced 12 reports suggesting shunt-related death. Of the 12 reports identified, 2 were of non-shunt devices misclassified as shunts leaving 10 shunt-related deaths.

TABLE E.5 Outcome as Reported for CSF Shunt Events in MDR and MAUDE Databases

	MDR		MAUDE	
Outcome	Number	Percent	Reported number	Percent
Death	15	0.9	8	0.3
Serious Injury	810	46.0	1,364	55.2
Malfunction	870	49.4	572	23.1
Other	67	3.8	528	21.4
Total	1,762		2,472	

In the MAUDE database, eight official reports listed outcome as "DEATH." The report narratives were examined in detail by the author. Four reports were found to state that the patient had died. In one instance, the reporter determined that the death was unrelated to the shunt. One report was the result of the filing of a malpractice suit alleging death related to the shunt. The other two patients died within 2 weeks of shunt operation and, therefore, would ordinarily be considered to have device-related mortality. Thus, of the eight official "DEATH" outcomes, six appeared to be definitely shunt related, one (the malpractice allegation) was possibly shunt related, and one was unrelated.

The report narratives were then text-searched for "DEATH" or "MORTALITY." Where death was mentioned but no details were available, the death was considered shunt related. When all reports indicating patient death, either in the outcome section of the official report or as a result of the text search, were adjudicated by the author, there were 11 deaths related to shunt complications. This includes any death within 30 days of shunt operation and excludes one patient who died 5 months postoperatively from an intracerebral hemorrhage.

This analysis of the reporting of shunt-related death suggests that both the outcome section of the reports and the automated text search of the entire narrative file result in overlapping and incomplete ascertainment of specific problems.

Because there were simply too many reports for individual review, and accepting the likely inaccuracies suggested by the detailed review of reporting of "DEATH," the computerized text searching of the MDR and MAUDE databases using the strategies described above was used to classify the reported complications using the classification scheme presented in Part 2. The MAUDE search done for Table E.6 utilized the strategy listed above, but used a different text searching program that was part of the preparation of data for the disproportionality analysis reported below, resulting in minor differences in identified mortality reports. The definition of "MALFUNCTION" in the "EFFECT TYPE" reporting analyzed above is differ-

TABLE E.6 Classification of Complications in the MDR and MAUDE Databases and Published Literature

		MDR		MAUDE		Literature	
Complication		#	%	#	%	#	%
Malfunction		201	12.9	526	21.3	179	14.1
	Occlusion	111	7.1	380	15.4	59	4.6
	Disconnection	77	5.0	125	5.1	16	1.3
	Migration	6	0.4	11	0.4	29	2.3
	Organ perforation	7	0.5	10	0.4	75	5.9
Infection		36	2.3	75	3.0	388	30.5
	infection	36	2.3	72	2.9	293	23.0
	Abdominal: cyst or peritonitis	0	0	3	0.1	7	0.6
	Shunt nephritis	0	0	0	0	88	6.9
Abdominal Cyst	(no infection)	0	0	0	0	43	3.4
Hemorrhage		29	1.9	54	2.2	55	4.3
Abdominal	metastasis	0	0	4	0.1	54	4.2
Pneumocephalus		9	0.6	6	0.2	28	2.2
Slit ventricles		442	28.4	109	4.4	33	2.6
Cardio-pulmonary		24	1.5	6	0.2	68	5.3
Mortality		12	0.8	5	0.2	12	0.9
Miscellaneous		802	51.6	1,687	68.2	412	32.4
Total		1,555		2,472		1,272	

ent from the definition of "MALFUNCTION" for the purposes of complication classification (some malfunctions would be called "SERIOUS INJURIES" while some would not), thus explaining the differences in the totals for "MALFUNCTION" in the two tables. This classification follows:

ECRI also maintains a Health Devices Alerts Data Base, which collects data, reports, and alerts "from a wide variety of national and international patient safety organizations, ECRI product evaluations, member hospital reports, and accident and forensic investigations, in addition to *FDA Enforcement Report* data and manufacturer notices." When searched with the following strategy ((((("CEREBROSPINAL FLUID" OR CSF OR VP OR V-P OR VA OR VENTR* OR HYDROCEPH* OR CNS OR CENTRAL) AND SHUNT) OR ("NEURO VALVE" OR PUDENZ OR "SHUNT KIT" OR "POSTERIOR FOSSA" OR OSV OR DELTA)))), there were 4 of 13 identified action items related to CSF shunts. A fifth was discovered serendipitously. Of 345 abstracts in published literature, 202 referred to CSF shunts. No alerts were identified.

ECRI defines action items as "reports of medical device problems, hazards, and recalls that have been verified by ECRI with the device manufacturer/distributor. Each Action Item includes ECRI's specific recommendations and instructions to help those who have the affected product take

the actions needed to prevent harm" (69). The nine unrelated action items involved devices such as knee prostheses, airways, and pacemakers that use some of the terms in the search but are not CSF shunt devices. The five action items involved risk of fracture of a right angle connector leading to a recall of unimplanted connectors (from a batch of 4,600 units), debris in metal connectors leading to a recall of 156 units, abnormally high operating pressure of valve leading to recall of all unimplanted units (number not specified), mislabeled closing pressure on valves leading to recall of unimplanted valves (from a total of 60,760 distributed), and the distribution of ventricular catheters without holes in them. The two most recent actions were in 1992 and 2004.

Data Mining Techniques

We applied disproportionality analysis techniques (see Appendix D) to the shunt subset of the MAUDE database. Shunt complications in the database were identified by searching the text of the narrative descriptions of adverse events in the database (the details are given in Appendix D of the main report). This analysis identified only two associations between specific manufacturers and adverse event reports. Table E.7 shows the results of the analysis, identifying an excess of catheter disconnections associated with products of Company A and an excess of catheter migration associated with products of Company B.

We could not identify any action such as a recall, safety alert, or publication possibly related to the migration events identified for Company B. In the case of company A, concern was expressed in the literature regarding fracture (included in our definition of disconnection) in papers published in 1992 and 1995 (60), (70), (71). These papers deal with predominantly pediatric populations. A change in the formulation of the catheter was made by the company in response to concerns about an excessive number of catheter fractures. As the public data in the MDR and MAUDE databases does not include the age of the patient, we could not determine if children were overrepresented in the adverse event reports. No author has

TABLE E.7 Disproportionality Analysis of CSF Shunt Events in MAUDE Database

N	E	RR	EBGM	Manufacturer	Event
91	47.2	1.93	1.85	COMPANY A	Disconnection
6	0.982	6.11	1.70	COMPANY B	Migration

NOTE: N = number of events reported, E = number of events expected in the absence of association, RR = raw relative risk estimate (N/E), EBGM (Empirical Bayes Geometric Mean) is an adjusted relative risk estimate. For details see Appendix C.

addressed the question of whether or not children are particularly susceptible to such fractures because of their activity levels.

Summary

Complications of CSF shunts have been the subject of clinical investigation since the first effective valve-regulated shunt was introduced in the 1950s. Important modifications in shunt procedures and design have been documented in the literature since that time. Since 1976, the FDA has collected reports from manufacturers and user facilities regarding death, serious injury, and malfunction related to CSF shunts. Analysis of these reports compared to the reports in the literature suggests that infections of CSF shunts have received much more attention in the literature than in the reports and that the problem of slit ventricles received greater attention in the MDR reporting system than in either the MAUDE system or the literature. The application of data mining techniques to the databases identified only one problem disproportionately associated with one manufacturer. There is suggestive evidence that this problem was also identified in the literature.

CONCLUSIONS

The tone for regulation of CSF shunts was set when the decision was made to classify them as Category II devices. This classification does not require premarket approval, which routinely requires submission of data from clinical studies. Viewed from today's perspective, this classification may seem unusually lax for a device that treats life-threatening conditions and may have malfunctions associated with death or disability.

The contrast with the cochlear implant (see Appendix F) is instructive. The first version of that device was approved through the premarket approval process in 1984 (P830069). Multiple design changes and adaptations have been approved since that time. The device has a low failure rate (between 0.8 percent and 0.3 percent per year), and the implantation infection rate is relatively low (1.6 and 4.1 percent in two recent reports) (72), (73). Yet 15 reports of meningitis created sufficient concern to result in studies that led to recall of one brand of implant. A subsequent study identified 26 cases of meningitis in 4,264 children with cochlear implants. This represents a substantial increase over the expected rate of meningitis, but is far below the rate of 7 to 9 percent for CSF infections as seen with CSF shunts (74). CSF shunts treat life-threatening disease, and their failure is associated with life-threatening complications. Cochlear implants treat a serious, but not life-threatening condition and rarely are associated with life-threatening complications. Although the focus on meningitis associated

with cochlear implants did not arise through the FDA device reporting system, FDA attention to the problem did generate significant change in available devices and management protocols to decrease the patient risk. No similar effort has been directed toward CSF shunt-related infection.

As of June 2003, there were 171 CSF shunt-related premarket notifications in the FDA database, resulting in decisions affirming "substantial equivalence." These decisions have allowed manufacturers to introduce many variations and modifications of the CSF shunt and its parts. For an important medical device with a relatively small market, the 510(k) notification approach may have been very effective and appropriate.

CSF shunts have been associated with very few manufacturing problems. The FDA has never recalled a shunt product. ECRI has issued only five health device alerts involving probably only several hundred actually distributed devices. The record suggests that the FDA's mechanisms for assuring sound manufacturing processes, biocompatibility, sterility, and basic function have worked well to minimize mechanical malfunction, faulty modifications in design, and errors in the manufacturing process.

There is good evidence of rational progress in the clinical history of CSF shunting. Both technical (surgical) and technologic (device) advances are real and persistent across the history of this undertaking. Technical successes include the evolution toward peritoneal distal catheters, cessation of implantation of short catheters (that require elective lengthening), and the realization that compulsive sterile technique is associated with decreased infection rates. Technical disappointments include endoscopic placement of ventricular catheters (75) and lack of clear superiority of frontal versus occipital trajectories (76). Technologic successes include the development of silastic, differential pressure valves, and pliant peritoneal catheters. Technologic disappointments have included flanged catheters, variations in ventricular catheter hole size, distal spring valves, polyethylene shunts, and flow-regulated valves (insofar as no expected decrease in obstruction rate was seen). Programmable valves and antimicrobial impregnation are recent developments for which no final conclusion can currently be reached. All of these developments have occurred in a relaxed federal regulatory environment.

However, shunts continue to have clinically significant, sometimes life-threatening complications. As noted at the STAMP conference, over 60 percent of shunted patients will experience a complication, most of which require surgical revision of the device. The rates of infection and malfunction have been stable for the past two decades, and there is no convincing evidence that they vary by brand or type of device. In the setting of premarket notification rather than premarket approval, the burden of identifying adverse events or complications for the purposes of assuring that safety and effectiveness are maintained falls predominantly outside the premarket

review system, with a small role for the formal postmarket surveillance system.

That postmarket surveillance system does not appear to have resulted in any important change in the safety or effectiveness of CSF shunts. Despite more than 4,000 reports of device problems, the majority of which resulted in patient injury or, rarely, death, there have been only four recalls identified. All were manufacturer initiated recalls related to manufacturing or labeling issues. With the exception of infection, which has received far greater attention in the published literature than in reports to the FDA, the device problems reported to the FDA have reflected the type and distribution of the problems reported in the medical literature. As a result, one could conclude that the time and effort involved in reporting and reviewing those reports, at least as implemented, thus far, have not resulted in any important change in the safety, effectiveness, or clinical use of CSF shunts.

The current structure of the adverse event reporting system makes it difficult to search it for the details necessary to analyze specific complications. Frequently, the data necessary to classify the adverse event report in a clinically useful manner is simply not present. Additionally, variation in the understanding of types of events and errors in product classification makes accurate analysis nearly impossible. However, it is clearly beyond reasonable expectations or the resources of the FDA to impose reporting rules that require adherence to carefully specified definitions, more detailed information, and rigorous error checking.

The application of data mining techniques did identify one manufacturing problem (excessive catheter fracture) that was contemporaneously identified in the medical literature.

These data raise several questions. One could argue that postmarket surveillance, in its present form, offers no benefit and could ask if it should be abandoned for these devices. Alternatively, the question remains whether or not a strengthened monitoring effort that would allow the identification of device-specific rates of infection and malfunction could result in further progressive improvement in both malfunction and infection rates. Is it a problem that the system monitors for serious device complications but does not feed this information into a system designed to identify and implement solutions to the problems? Has the system been lulled into inaction by accepting as inevitable the relatively high rates of complications associated with CSF shunts?

For the present, the burden of identifying problems associated with CSF shunts and searching for solutions to those problems rests with the informal system of clinical observation and research. While real gains have been made and the life of a hydrocephalic child is markedly different than a generation ago, there is clearly much more to learn. Recent flow-controlled valves more closely emulate best available concepts of CSF physiology, but

have failed to reduce rates of obstruction. This failure has heightened collective awareness concerning our incomplete understanding of CSF physiology and the pathophysiology of hydrocephalus. The question of whether or not a higher level of FDA regulation and more intense focus on the CSF shunt would have resulted in a shunt with lower risk of infection and malfunction cannot be answered from this retrospective look at the problem. It is, however, an important question worthy of further exploration.

REFERENCES

1. Bondurant CP, Jimenez DF. Epidemiology of cerebrospinal fluid shunting. Pediatr Neurosurg 1995;23(5):254–258.
2. Drake JM, Kestle JR, Tuli S. CSF shunts 50 years on—past, present and future. Child's Nerv Syst 2000;16(10-11):800–804.
3. Brian J, Warner D. 1997. Atlas of anesthesia: Scientific principles of anesthesia. Miller R, Schwinn DA, eds.
4. Digre K. Idiopathic intracranial hypertension headache. Current Pain and Headache Reports. 6(3):217–225.
5. Aschoff A, Kremer P, Hashemi B, Kunze S. The scientific history of hydrocephalus and its treatment. Neurosurg Rev 1999;22(2-3):67–93.
6. Iantosca MR, Hader WJ, Drake JM. Results of endoscopic third ventriculostomy. Neurosurg Clin N Am 2004;15(1):67–75.
7. Engelman RM, Ransohoff J, Cortes LE, Spencer FC. Complications of ventriculoatrial shunting for hydrocephalus requiring cardiac operation. Annals of Thoracic Surgery 1969;8(5):464–469.
8. Becker DP, Nulsen FE. Control of hydrocephalus by valve-regulated venous shunt: avoidance of complications in prolonged shunt maintenance. J Neurosurg 1968 March;28(3): 215–226.
9. Muke R, Glashoff M. The longitudinal increase of the internal jugular vein and the upper v. cava as measured between the mastoid to the heart: parameter for timing the reoperation after ventriculocardiostomy (author's transl). Monatsschr Kinderheilkd 1976 April;124(4):157–161.
10. Svien HJ, Dodge HW Jr., Lake CF. Ventriculomastoid shunt in the management of obstruction to the aqueduct of sylvius in the adult; report of case. Mayo Clinic Proceedings 1952 May;2127(11):215–218.
11. Sharkey PC. Ventriculosagittal-sinus shunt. Journal of Neurosurgery 1965 April 22;362–367.
12. Smith GW, Moretz WH, Pritchard WL. Ventriculo-biliary shunt; a new treatment for hydrocephalus. 1958:Surgical Forum 9:701–705.
13. Ransohoff J. Ventriculo-pleural anastomosis in treatment of midline obstructional neoplasms. Journal of Neurosurgery. 1954 May;11(3):295–298.
14. Jackson IJ, Snodgrass SR. Peritoneal shunts in the treatment of hydrocephalus and increased intracranial pressure: a 4-year survey of 62 patients. Journal of Neurosurgery 1955 May; 12(3):216–222.
15. Cochrane DD, Kestle JR. The influence of surgical operative experience on the duration of first ventriculoperitoneal shunt function and infection. Pediatr Neurosurg 2003 June;38(6):295–301.
16. Griebel R, Khan M, Tan L. CSF shunt complications: an analysis of contributory factors. Child's Nerv Syst 1985;1(2):77–80.

17. Guertin SR. Cerebrospinal fluid shunts. Evaluation, complications, and crisis management. Pediatr Clin North Am 1987;34(1):203–217.
18. McGirt MJ, Leveque JC, Wellons JC3, Villavicencio AT, Hopkins JS, Fuchs HE, et al. Cerebrospinal fluid shunt survival and etiology of failures: a seven-year institutional experience. Pediatr Neurosurg 2002;36(5):248–255.
19. Piatt JH Jr., Carlson CV. A search for determinants of cerebrospinal fluid shunt survival: retrospective analysis of a 14-year institutional experience. Pediatr Neurosurg 1993;19(5):233–241.
20. Tuli S, Drake JM. Multiple shunt failures: an analysis of relevant features. Child's Nerv Syst 1999;15(2-3):79.
21. Pollack IF, Albright AL, Adelson PD. A randomized, controlled study of a programmable shunt valve versus a conventional valve for patients with hydrocephalus. Hakim-Medos Investigator Group. Neurosurgery 1999 December;45(6):1399–1408.
22. Drake JM, Kestle J. Rationale and methodology of the multicenter pediatric cerebrospinal fluid shunt design trial. Pediatric Hydrocephalus Treatment Evaluation Group. Child's Nerv Syst 1996;12(8):434–447.
23. Drake JM, Kestle J. Determining the best cerebrospinal fluid shunt valve design: the pediatric valve design trial. Neurosurgery 1996;38(3):604–607.
24. Drake JM, Kestle JR, Milner R, Cinalli G, Boop F, Piatt J Jr., et al. Randomized trial of cerebrospinal fluid shunt valve design in pediatric hydrocephalus. Neurosurgery 1998;43(2):294–303.
25. Borgbjerg BM, Gjerris F, Albeck MJ, Borgesen SE. Risk of infection after cerebrospinal fluid shunt: an analysis of 884 first-time shunts. Acta Neurochir (Wien) 1995;136 (1-2):1–7.
26. Drake JM. Shunt infections. J Neurosurg 1996;855:985–986.
27. Walters BC. Cerebrospinal fluid shunt infection. Neurosurg Clin N Am 1992;3(2):387–401.
28. Corlett K. Septicaemia and meningitis in hydrocephalus. Report of a case complicating ventriculo-atrial shunt with a Spitz-Holter valve. Northwest Medicine 1960 November;59:549–551.
29. Kulkarni AV, Rabin D, Lamberti-Pasculli M, Drake JM. Repeat cerebrospinal fluid shunt infection in children. Pediatr Neurosurg 2001;35(2):66–71.
30. Bryant MJ, McEniery J, Walker DG, Campbell R, Lister B, Sargent P, et al. Preliminary study of shunt related death in paediatric patients. J Clin Neurosci 2004;11(6):614–615.
31. McGirt MJ, Zaas A, Fuchs HE, George TM, Kaye K, Sexton DJ. Risk factors for pediatric ventriculoperitoneal shunt infection and predictors of infectious pathogens. Clin Infect Dis 2003;36(7):858–862.
32. Enger PO, Svendsen F, Wester K. CSF shunt infections in children: experiences from a population-based study. Acta Neurochir (Wien) 2003;145(4):243–248.
33. Tuli S, Tuli J, Drake J, Spears J. Predictors of death in pediatric patients requiring cerebrospinal fluid shunts. J Neurosurg Spine 2004;100(5):442–446.
34. Cochrane DD, Kestle J. Ventricular shunting for hydrocephalus in children: patients, procedures, surgeons and institutions in English Canada, 1989-2001. European Journal of Pediatric Surgery 2002 December;12 Suppl 1:S6–S11.
35. Schreffler RT, Schreffler AJ, Wittler RR. Treatment of cerebrospinal fluid shunt infections: a decision analysis. Pediatr Infect Dis J 2002;21(7):632–636.
36. Darouiche RO. Treatment of infections associated with surgical implants. N Engl J Med 2004;350(14):1422–1429.
37. Smith ER, Butler WE, Barker FG. In-hospital mortality rates after ventriculoperitoneal shunt procedures in the United States, 1998 to 2000: relation to hospital and surgeon volume of care. J Neurosurg Spine 2004 February;100(2):90–97.

38. Smith ER, Butler WE, Barker FG. In-hospital mortality rates after ventriculoperitoneal shunt procedures in the United States, 1998 to 2000: relation to hospital and surgeon volume of care. [see comment]. Journal of Neurosurgery Spine 2004 February;100(2): 90–97.
39. Blum J, Schwarz M, Voth D. Antibiotic single-dose prophylaxis of shunt infections. Neurosurg Rev 1989;12(3):239–244.
40. Faillace WJ. A no-touch technique protocol to diminish cerebrospinal fluid shunt infection. Surg Neurol 1995;43(4):344–350.
41. Fitzgerald R, Connolly B. An operative technique to reduce valve colonisation. Z Kinderchir 1984;39 Suppl 2:107–108.
42. Gardner P, Leipzig TJ, Sadigh M. Infections of mechanical cerebrospinal fluid shunts. Curr Clin Top Infect Dis 1988;9:185–214.
43. Kulkarni AV, Drake JM, Lamberti-Pasculli M. Cerebrospinal fluid shunt infection: a prospective study of risk factors. J Neurosurg 2001;94(2):195–201.
44. Arze RS, Rashid H, Morley R, Ward MK, Kerr DN. Shunt nephritis: report of two cases and review of the literature. Clin Nephrol 1983;19(1):48–53.
45. Futrakul P, Surapathana LO, Campbell RA. Review of shunt nephritis. J Med Assoc Thai 1970 April;53(4):265–274.
46. Meadow R. Shunt nephritis: renal disease associated with infected ventriculo-atrial shunts. Dev Med Child Neurol 1973 February;15(1):83-84.
47. Bryant MS, Bremer AM, Tepas JJ3, Mollitt DL, Nquyen TQ, Talbert JL. Abdominal complications of ventriculoperitoneal shunts. Case reports and review of the literature. Am Surg 1988;54(1):50–55.
48. Ersahin Y, Mutluer S, Tekeli G. Abdominal cerebrospinal fluid pseudocysts. Child's Nerv Syst 1996;12(12):755–758.
49. Rainov N, Schobess A, Heidecke V, Burkert W. Abdominal CSF pseudocysts in patients with ventriculo-peritoneal shunts. Report of fourteen cases and review of the literature. Acta Neurochir (Wien) 1994;1271-1272:73–78.
50. Gaskill SJ, Marlin AE. Pseudocysts of the abdomen associated with ventriculoperitoneal shunts: a report of twelve cases and a review of the literature. Pediatr Neurosci 1989;15(1):23–26.
51. Govender ST, Nathoo N, van Dellen JR. Evaluation of an antibiotic-impregnated shunt system for the treatment of hydrocephalus. [see comment]. Journal of Neurosurgery 2003 November;99(5):831–839.
52. Govender ST, Nathoo N, van Dellen JR. Evaluation of an antibiotic-impregnated shunt system for the treatment of hydrocephalus. J Neurosurg 2003;99(5):831-839.
53. Hammock MK, Milhorat TH, McClenathan JE. Expanding ventricular shunts for hydrocephalus in infancy and childhood. Dev Med Child Neurol Suppl 1975;(35):89–93.
54. Bridges N, Rifkinson-Mann S, Handler M, Epstein F. Planning ventriculoperitoneal shunts in infants and small children. Pediatr Neurosci 1988;14(4):191-195.
55. Goldenberg TM, Pritz MB. A simple method for distal catheter lengthening of ventriculoperitoneal shunts. Technical note. J Neurosurg 1992 November;77(5):810–811.
56. Mittal P, Chand M, Chhabra DK. A simplified technique for lengthening peritoneal catheters. Br J Neurosurg 1992;6(5):475–476.
57. Ninomiya H, Yoshimine T, Maruno M, Kato A, Hayakawa T. A peritoneal marker for optimal timing of ventriculo-peritoneal shunt revision in early childhood. Neurol Res 1998 September;20(6):526–528.
58. Couldwell WT, LeMay DR, McComb JG. Experience with use of extended length peritoneal shunt catheters. Journal of Neurosurgery 1996 September;85(3):425-427.
59. Langmoen IA, Lundar T, Vatne K, Hovind KH. Occurrence and management of fractured peripheral catheters in CSF shunts. Child's Nerv Syst 1992 June;8(4):222–225.

60. Cuka GM, Hellbusch LC. Fractures of the peritoneal catheter of cerebrospinal fluid shunts. Pediatr Neurosurg 1995;22(2):101–103.
61. Ramsey DB, Chadduck WM. Premature fractures of platinum-cured Silastic shunts. Child's Nerv Syst 1992 October;8(7):406–410.
62. CDRH (Center for Devices and Radiological Health). Device Classes. Web Page. Online 2002 November 21; Available from: URL: http://www.fda.gov/cdrh/devadvice/3132.html#class_3.
63. Pena C, Bowsher K, Samuels-Reid J. FDA-approved neurologic devices intended for use in infants, children, and adolescents. Neurology 2004;63(7):1163–1167.
64. CDRH. Shunt Technology: Challenges and Emerging Directions. Online 1999 January 8; Available from: URL: http://www.fda.gov/cdrh/stamp/shuntconf.pdf.
65. CDRH. Releasable 510(k) Database. Web Page. Online 2005 May 5; Available from: URL: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmn.cfm.
66. CDRH. File Layout for Releasable 510(k)s. Web Page. Online 2005 June 6; Available from: URL: http://www.fda.gov/cdrh/pmndoc.html.
67. CDRH. 510(k) Summary for HP Valve System (K974739). Online 1997 December 18; Available from: URL: http://www.fda.gov/cdrh/pdf/k974739.pdf.
68. CDRH. Device Advice: Postmarket Surveillance Studies. Web Page. Online 1 A.D. June 8; Available from: URL: http://www.fda.gov/cdrh/devadvice/352.html.
69. ECRI. Health Device Alerts. Online 2003 December 1; Available from: URL: http://www.ecri.org/demo/hdimagingdemo/hdimgfaq.html.
70. Ramsey DB, Chadduck WM. Premature fractures of platinum-cured Silastic shunts. Child's Nerv Syst 1992 October;8(7):406–410.
71. Langmoen IA, Lundar T, Vatne K, Hovind KH. Occurrence and management of fractured peripheral catheters in CSF shunts. Child's Nerv Syst 1992 June;8(4):222–225.
72. Cunningham CD, III, Slattery WH, III, Luxford WM. Postoperative infection in cochlear implant patients. Otolaryngol Head Neck Surg 2004 July;131(1):109–114.
73. Yu KC, Hegarty JL, Gantz BJ, Lalwani AK. Conservative management of infections in cochlear implant recipients. Otolaryngol Head Neck Surg 2001 July;125(1):66–70.
74. Reefhuis J, Honein MA, Whitney CG, Chamany S, Mann EA, Biernath KR, et al. Risk of bacterial meningitis in children with cochlear implants. N Engl J Med 2003 July 31;349(5):435–445.
75. Kestle JR, Drake JM, Cochrane DD, Milner R, Walker ML, Abbott R 3rd, et al. Lack of benefit of endoscopic ventriculoperitoneal shunt insertion: a multicenter randomized trial. J Neurosurg 2003;98(2):284–290.
76. Albright AL, Haines SJ, Taylor FH. Function of parietal and frontal shunts in childhood hydrocephalus. J Neurosurg 1988;69(6):883–886.

F

Cochlear Implants in Children: A Review of Reported Complications, Patterns of Device Failure, and Assessment of Current Approaches to Surveillance

John K. Niparko M.D., Janice Leung A.B.,**
*Debara L. Tucci M.D.,** Martin J. Burton M.D., F.R.C.S.,****
*Eric A. Mann M.D., Ph.D.*****

INTRODUCTION

Impairment of hair cell function induces profound deafness in approximately 0.3 percent of children younger than 5 years.[1,2] In deafness, hair cells of the inner ear fail to trigger auditory nerve fibers in the presence of sound. However, large reserves of auditory nerve fibers exist even in the ear of the profoundly deaf. Furthermore, these nerve fibers retain the ability to respond to electrical activation. Cochlear implants could potentially affect the auditory rehabilitation of an estimated 200,000 United States children with advanced levels of deafness as indicated by a failure to achieve critical milestones in speech and language using conventional hearing aids.

While the impact of hearing loss in an adult varies considerably with the severity of hearing loss and with lifestyle choices, the impact of an advanced level of hearing loss in infancy and early childhood can dramatically affect developmental learning. Because most domains of communication and language learning are subserved by early access to the phonology of speech, deafness effects can extend to the acquisition of visual-language reception (reading) and visual-language production (writing), as well as the constructs of spoken language. A hearing 5-year-old child, for example, has

*Johns Hopkins University.
**Duke University.
***Oxford University.
****Center for Devices and Radiological Health, U.S. Food and Drug Administration.

a vocabulary that ranges between 5,000 and 26,000 words. In comparison, a deaf child of the same age usually has access to a vocabulary of about 200 words and limited ability to structure a spoken sentence.[3] Given the substantial impact of deafness on development and the potential benefit of restored hearing, there are risks of underestimating the importance of potential complications associated with a device-oriented approach to deafness. Complications associated with the implantation procedure and device malfunction may arise during critical stages of language acquisition, before a child can be expected to report on their experience with an implanted device.

The cochlear implant is best characterized as a device that provides access to sound. The device enables the hearing pathway to respond to environmental and speech sounds, providing informational cues from the surroundings and from others through direct, electrical activation of auditory nerve fibers tuned to frequencies that span the spectrum of practical hearing.

In October 2004, the U.S. Food and Drug Administration (FDA) developed a website that contains general information on hearing physiology (including animated graphics), information on how a cochlear implant functions, as well as FDA regulatory approvals for these devices. The reader is referred to this website as a comprehensive resource for background information on cochlear implants: http://www.fda.gov/cdrh/cochlear/index.html.

Three different manufacturers of cochlear implant systems provide currently available devices. All three product devices consist of similar component parts

1. An external unit comprised of a microphone, speech processor (Figures F.1 and F.2), and batteries to drive the system.
2. An implanted receiver and electronics package (Figure F.3) with connecting leads that feed an electrode array (Figure F.4).

The design of the electrode array must incorporate biocompatibility, mechanical stability, practical fabrication, and minimize insertion trauma. From a surgical point of view, efforts to reduce insertion trauma must be accomplished at the materials and design levels, as well as through the surgical technique.

For the past two decades, mastoid-implantable internal devices with leads to electrical arrays placed in the basal turn of the cochlea have been applied to deaf children as an increasingly large proportion of all cochlear implants placed (Figures F.5 and F.6). As of 2003, more than half of all newly implanted devices have been placed in children under age 5. It is estimated that approximately 7,500 to 10,000 United States children have received a multichannel cochlear implant prior to the age of 5 years out of

FIGURE F.1 Ear-level processor. (Courtesy of Cochlear Americas Corporation.)

FIGURE F.2 Body-worn processor. (Courtesy of Cochlear Americas Corporation.)

a worldwide population of approximately 90,000 recipients as of February 2005 (synthesis of verbal communication with the three major cochlear implant manufacturers: Advanced Bionics Corporation, Cochlear Corporation, and Med El Corporation, February 2005).

Auditory thresholds of cochlear-implanted children allow access to auditory information beyond that available to deaf children who routinely use conventional amplification (hearing aids). Lowered hearing thresholds offer a substrate for auditory therapy.[4] Through developmental learning in the early, formative years, auditory centers of the brain appear capable of processing the additional information from the implant in ways that are not possible at later developmental stages. Speech comprehension and oral lan-

FIGURE F.3 An implanted receiver and electronics package. (Courtesy of Advanced Bionics Corporation.)

FIGURE F.4 An electrode ray. (Courtesy of Advanced Bionics Corporation.)

guage development after implantation occur at a rate that parallels that of normal hearing peers, although gaps due to early deprivation often persist. Phonologic access afforded by of the cochlear implant to children has set the stage for several global perceptions of the intervention:

- the cochlear implant represents one of many innovative technologies that enable the rapid transfer of processed information from sound to comprehension;
- implant technology represents an alliance of informational processing strategies that utilize both manufactured and natural neural circuits;

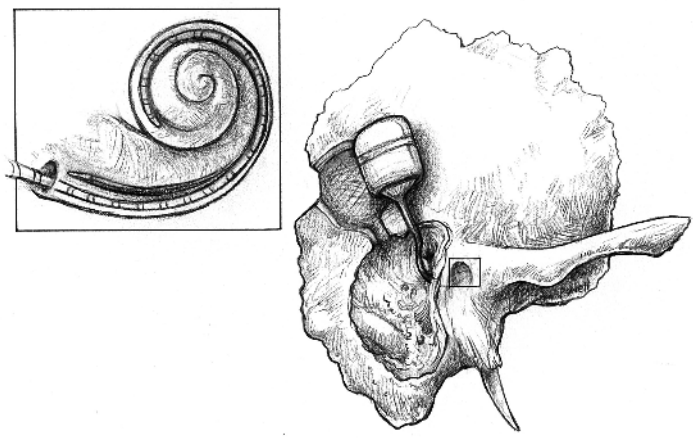


FIGURE F.5 An implanted electronics and receiver package connected to an electrode ray, which is inserted through the cochlea. (Used with permission of Lippincott Williams & Wilkins. Originally appeared in *Cochlear Implants: Principles and Practices*, 2000. Niparko J, Kirk KI, Mellon NK, eds.)

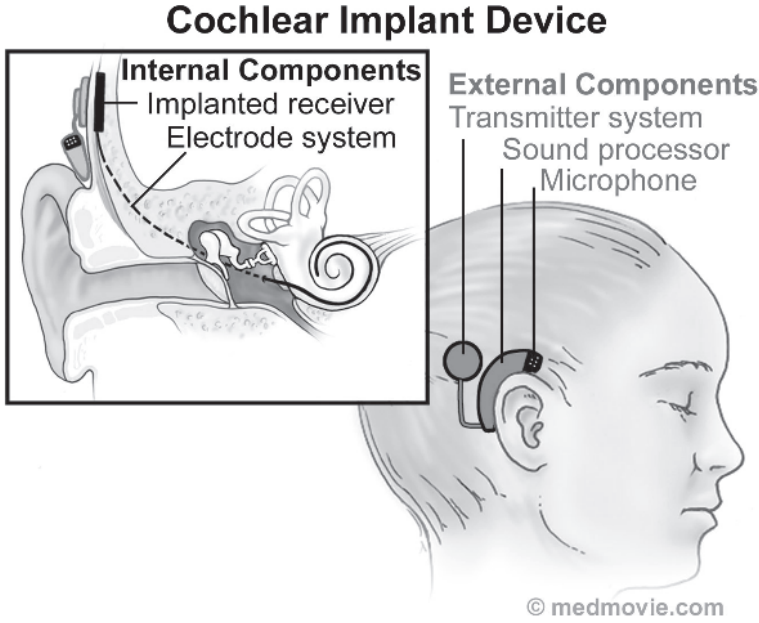


FIGURE F.6 The cochlear implant system comprised of its internal and external components. (Courtesy of Medmovie.com.)

- to the extent that a cochlear implant can encode the sounds of speech with precision, the device can provide opportunities for developmental and oral language learning in young children with implications for psychosocial development, scholastic achievement, and life chances; and
- potentially dramatic, life-altering outcomes following early cochlear implantation have fostered high media visibility and enthusiasm about the benefits of early implantation.

Against a two-decade old background of a generally positive global perception of clinical effects of cochlear implants in deaf children, a more open acknowledgement of potential harms has emerged in recent years. This summary provides background, peer-reviewed information regarding current risks posed to implant recipients and suggests approaches to improve surveillance of complications associated with cochlear-implantable devices in children.

We begin with a description of considerations for candidacy selection and then review current understanding of complications and underlying mechanisms. We close with an assessment of the current state of device surveillance and propose several approaches to addressing the considerable challenge of tracking the health of children with cochlear implants.

CANDIDACY EVALUATION: MEDICAL, OTOLOGIC AND RADIOLOGIC ASSESSMENT

General Medical and Otologic Assessment

To date, most cochlear implantations have been performed in children over the age of 2, though recent trends have shifted applications to ever younger patients. The main concerns with implanting infants and toddlers relate to the unreliability of audiologic testing at these ages, the prevalence of otitis media, challenges in the rehabilitation process, surgical obstacles posed by smaller tolerances in surgically approaching the cochlea. Nonetheless, centers have demonstrated promising results with few surgical complications.[5,6,7,8,9] Moreover, outcome analyses seem to suggest the value in implanting at earlier ages. Zwolan and colleagues reviewed their series of 295 children implanted between 12 months and 10 years of age and observed that children implanted at younger ages experienced greater gains in speech perception over time than children implanted at a later stage.[10] Robbins and colleagues[11] noted that children implanted prior to the age of 19 months carry the highest potential for acquiring auditory skills at rates

that are not statistically different from their normal-hearing peers. Likewise, Schauwers and colleagues[12] found smaller delays in the onset of babbling with earlier implantation, and Govaerts and colleagues[13] found that implantation before the age of 2 was important in achieving optimal results. These case series of children suggest that implant-based percepts promote developmental learning in keeping with constructs of critical-period dictates of early language development.

It does not appear that earlier implantation is associated with higher device-related complications. For example, a review of 34 cochlear implant complications in the Johns Hopkins cohort of 1,030 patients found that 51 percent of implants were placed in children under the age of 4 years. Device failure was found to occur in children under the age of 5 years in 11 of the 34 cases (33 percent).

In addition to age considerations, the child must undergo a series of tests to ensure the proper candidacy for the procedure. Evaluation should include a complete medical history with appropriate laboratory studies and an assessment of the patient's general health and ability to endure a general anesthetic for the necessary mastoid surgery. For children under the age of 9 to 12 months, general anesthetic may carry increased risk;[14] therefore, the benefits of earlier implantation must be carefully assessed against these risks. Although implantation under a local anesthetic has been described, this approach is usually not recommended because it constrains the soft tissue dissection behind the mastoid required for embedding the internal device.

Patients must be physically and psychologically capable of completing the course of recommended programming and therapy. Personality traits and family dynamics that predict program engagement should be assessed. Psychological assessment may be indicated to screen for psychopathology and organic brain disease. However, children with developmental delays and other limitations or disabilities should not be barred from implantation. While such children may not experience the same gains as deaf children without other functional limitations, numerous studies have shown considerable benefit is still possible.[15,16,17,18]

Both the chronology of deafness and the history of amplification use can help determine the choice of ear to be implanted. Previous otologic operations should be documented, as well as any abnormalities or diseases. In particular, a history of meningitis should prompt a discussion of methods for implanting a cochlea that may be partially or fully ossified as a result of meningitic-related inflammation. While post-meningitic deaf children were previously thought to perform at less impressive levels after implantation due to the neuropathologic consequences of the disease at the level of the inner ear, Francis and colleagues[19] found no significant delays in their cognitive or speech perception performance, with the exception of

those children who exhibited evidence of meningitic-related hydrocephalus. Data from this case series of 30 meningitis-deafened children suggest that central factors hold sway in predicting audiologic performance and that ossification of the cochlea does not prevent good outcomes.

Most children who present for cochlear implantation will likely have some history of acute otitis media (AOM). However, this does not constitute a clinical contraindication currently, as long as the condition is under control at surgery. The surgeon, however, should be prepared for an inflamed middle ear mucosa that may complicate and lengthen the surgery.[20] Based on clinical experience, ventilation tubes may be removed before implantation, but should be left in if the child has frequent recurrent episodes of AOM. Luntz and colleagues[21] suggest the continuous use of ventilation tubes until the child has outgrown susceptibility to AOM based on a study.

In audiologic testing, the cochlear implant candidate should have puretone averages (PTA) greater than 90 dB and speech understanding scores of up to 50 percent on sentence testing, though recent work has suggested that children who retain greater residual hearing may still also significantly benefit from implantation.[22] Such guidelines, however, are less compelling as younger candidates are considered. The required testing may prove difficult in young children. For such children, severe to profound levels of hearing loss, severe delays in verbal language acquisition, and substantial elevations in thresholds even with the use of hearing aids may indicate the need for an implant.[23]

Special consideration should be given to patients for whom magnetic resonance imaging (MRI) may be needed in the future. MRI is conventionally contraindicated in patients with magnetic devices. Recently, devices compatible with low-strength MRI (0.2 Tesla) and devices which can be rendered MRI compatible (by a minor surgical procedure to remove the magnet should the need for an MRI arise) have become available from some of the manufacturers.[24,25,26] Even with magnetic devices left in place and intact, though, at least three reports have suggested that MRI can be safely performed.[27,28,29] Nonetheless, at least three adverse events are under investigation.

Etiologic Assessment

Determining the cause of a child's hearing loss can reveal information about the expected histopathology of the inner ear. Although many patient factors are deemed important in predicting success of speech recognition with the cochlear implant, survival of the first-order neurons is thought to be of particular importance. Second, recognition of factors that are associated with cochlear abnormalities (e.g., congenital malformations or ossifi-

cation) is critical for surgical planning and for patient and family counseling before implantation.

Nadol's studies[30] of almost 100 temporal bones from patients with documented profound sensorineural hearing loss reveal patterns of spiral ganglion cells (SGC) survival that are consistent across diagnostic categories. Residual SGC counts were highest in individuals who were deafened by aminoglycoside ototoxicity or sudden idiopathic sensorineural hearing loss and least in those deafened by postnatal viral labyrinthitis or congenital causes. Counts for the two other etiologic categories—temporal bone neoplasms and bacterial labyrinthitis—fall in between. Age at time of death and duration of deafness were less predictive of SGC survival than was the cause of hearing loss.

Labyrinthitis ossificans, or new bone formation in the inner ear, is a common finding in the temporal bones of patients who are deafened by bacterial meningitis. Quantitative assessment of 11 temporal bones of these patients by Nadol revealed a significant negative correlation between SGC survival and the presence of bony occlusion.[30] However, even in segments with severe bony occlusion, significant numbers of SGCs remained. In a study of temporal bones from previously implanted patients, Linthicum and colleagues[31] found that useful auditory sensations are reported by individuals whose temporal bones were found to have as few as 10 percent of the normal complement of cells. Although the presence of ossification is not considered a contraindication to implantation, the degree of ossification as demonstrated on imaging studies preoperatively should correlate with SGC survival and help guide the implant team in selecting an ear for implantation.

Radiologic Assessment

Radiologic imaging is an essential part of the evaluation of the cochlear implant candidate. High-resolution computerized tomography (HRCT) scans of the temporal bone help to define the surgical anatomy and provide information about cochlear abnormalities that can aid the surgeon in surgical planning and patient counseling. Temporal bone CT scans should be obtained and reviewed for evaluation of temporal bone anatomy with attention to the degree of mastoid pneumatization, position of vascular structures, middle ear anatomy, and position of the facial nerve.[32] Scans are also examined for evidence of cochlear malformation, cochlear ossification, enlarged vestibular aqueduct, and other inner ear and skull base anomalies. An absolute contraindication to cochlear implantation detectable by HRCT is the absence of the cochlea in Michel's aplasia.

Although HRCT is the gold standard for evaluating most aspects of temporal bone anatomy, MRI is ideal in imaging soft tissue structures such as the membranous labyrinth and nerves. MRI can identify the presence or

absence of fluid within the cochlear turns and the size of the cochlear and vestibular nerves within the internal auditory canals. MRI is superior to HRCT in determining cochlear obstruction due to non-ossified scarring. One disadvantage to using MRI in children, though, is the need for sedation.

CRITERIA FOR DEFINING COMPLICATIONS IN COCHLEAR IMPLANTATION

A number of classification schemes have been developed to help define complications in the cochlear implantation process. Cohen and colleagues[33] labeled "major" complications as those requiring additional surgery or hospitalization for treatment or correction, while "minor" complications resolve with minimal or no treatment. Exceptions to this distinction include facial nerve palsy or paralysis, considered to be a "major" complication even if no further surgery or inpatient treatment is required. As examples, they cite flap necrosis and improper electrode placement as "major" complications and dehiscence of incisions, infection, facial nerve stimulation, dizziness, and pedestal problems as "minor" complications. The initial reports revealed the rate of "major" and "minor" complications to be 8 percent and 4.3 percent, respectively, but later analyses found the rates to be 5 percent and 7 percent, suggesting a decrease in major complications with experience over time.[34]

Determining the stage at which complications arise can also be helpful. Luetje and Jackson[35] separated "surgical" complications from "non-surgical" complications. "Surgical" complications were identified as skin flap problems, facial nerve injury and stimulation, and infection. "Non-surgical" complications consisted of device failure, delayed stimulation, educational deficiencies, poor compliance by the family unit, behavioral problems, and socioeconomic disadvantages. In a review of 55 children, no "surgical" complications were found whereas "non-surgical" problems occurred, the most common being device failure in 10.9 percent of the group.

Finally, the timing of events is of interest. Kempf and colleagues[36] characterized "early" complications as those that arose within 3 months of surgery and "delayed" complications as those that occurred after this time period. In their retrospective analysis of 366 children, "early" complications such as flap problems, electrode dislocation, facial nerve problems, and incorrect insertion of the electrode, were found in 1–2.5 percent of children. "Delayed" complications, for example, otitis media and facial nerve stimulation, occurred in 14 percent of the children.

Although children were indeed once thought to be at greater risk than adults of major and minor complications from cochlear implantation, stud-

ies have, in fact, suggested no significantly heightened risk in the pediatric population. In a series of 309 children who were implanted with the Nucleus device by 25 surgeons in North America before 1991, the total complication rate (major and minor) was 7 percent, which compared favorably with the adult rate of 12 percent. The incidence of complications was lower in children older than 7 years of age. However, the relatively low rate of operative complications in the pediatric population as reported in this study may have reflected the greater experience of surgeons who initially performed pediatric cochlear implants.[44, 37]

SURGICAL ISSUES RELATED TO COMPLICATIONS

Cochlear Implantation Surgical Procedures

Implantation of the young child requires specific knowledge of the unique anatomy of the temporal bone in this age group and of the impact of skull growth on the implanted device. Although temporal bone growth has been shown to continue through adolescence, anatomy of the facial recess is fully developed at birth.[38,39] The most significant developmental changes are in the size and configuration of the mastoid cavity, which has been shown to expand in width, length, and depth from birth until at least the teenage years. Growth of the mastoid during this time parallels the growth patterns of the skull, with two periods of rapid development: one starts at birth and continues through early childhood, and the other occurs at puberty. From 1 year of age to adulthood, the average mastoid can be expected to grow 2.6 cm in length, 1.7 cm in width, and 0.9 cm in depth for males and 2.0 cm in length, 1.7 cm in width, and 0.8 cm in depth for females. Based on these measurements, it has been recommended that 2.5 cm of electrode lead redundancy in the mastoid is necessary to accommodate head growth while avoiding electrode extrusion.[40,41]

Investigation in the young primate has demonstrated that cochlear implantation had no adverse effects on skull growth.[42,43] Moreover, the electrode appears to remain in a stable position with no migration over time.[44] These observations strongly suggest that lateral skull base development occurs in a pattern that circumscribes the implanted device, with soft-tissue anchoring of connecting leads.

As for all otologic surgery in children, the surgeon should remember that the lack of development of the mastoid tip, narrow tympanic ring, and lack of subcutaneous tissue in infants and toddlers place the main trunk of the facial nerve just below the skin, where it is easily injured by an incorrectly placed incision. Design of the postauricular skin flap is particularly important. In younger children, who have a thin scalp, elevation of the postauricular tissue in continuity with the skin flap may protect from flap

necrosis secondary to magnet pressure.[45] In older children, the lateral skull is usually thick enough to permit the creation of an adequate well for the receiver/stimulator. In younger children, in whom the skull is much thinner, the bone is often drilled to the level of the dura, or a mobile island of thin bone can be created over the dura in the center of the well for protection. Alternatively, many surgeons make attempts to thin the skull to approximate, but not reach, the level of the dura. Retention sutures are often placed between the bone and dura. Electrode insertion and closure are similar to the procedures in the adult.

A new development in the surgical procedure is minimal access surgery, proposed by O'Donoghue and Nikolopoulos.[46] With this technique, a short, oblique, and straight postauricular incision of a length no greater than 3 cm is made without shaving any hair, thereby minimizing flap infection and flap necrosis. The authors posit improved aesthetic quality of this procedure that can reduce the psychological trauma of the intervention and can translate into increased acceptance of cochlear implants by children and their families. In general there has been a move to smaller incisions in placing cochlear implants in children as guided by these considerations rather than in response to demonstrated complications.

Implantation of Special Populations

Cochlear Ossification

Labyrinthitis ossificans results from severe inflammation of the inner ear and can be associated with a variety of pathology, including viral or bacterial labyrinthitis, advanced otosclerosis, trauma, autoimmune inner ear disease, occlusion of the labyrinthine artery, and leukemia or other tumors of the temporal bone.[47] Labyrinthitis ossification presents one of the greatest challenges to effective, safe cochlear implantation. In children, the most likely cause of cochlear ossification is meningitis. Twenty percent of children acquire profound bilateral sensorineural hearing loss prior to the age of 3 years; 90 percent of these cases are meningitic in origin.[48] Green and colleagues demonstrated that ossification due to meningogenic labyrinthitis extended further into the cochlea than ossification due to other causes. The extra bone growth makes the insertion of the electrode a difficult process.[47] In addition, the stimulation of surviving neural elements may be compromised by the bony obliteration, and histopathololgic reports have shown an association between the degree of bony occlusion and a decreased number of surviving SGCs,[49] particularly in cases of bacterial meningitis. For these reasons, patients with labyrinthitis ossificans were often thought to perform at lower levels than those without ossification.

Nonetheless, certain factors make successful implantation possible. In

most cases, ossification involves only the most basal portion of the cochlea, allowing complete electrode insertion.[50] A significant if decreased number of neurons can also remain in ossification.[51] El-Kashlan and colleagues[52] and Steenerson and Gary[53] therefore found that children with post-meningitic hearing loss and cochlear ossification could attain significant benefit from their implants, although children without ossification were likely to perform better. Still, other studies demonstrate that ossified and non-ossified children perform equally well.[54] A key factor for success may be the timing of implantation. Ossification may appear as early as 2 months following meningitis, leaving a small time period during which electrode insertion is optimal.[55] As mentioned previously, however, central nervous system sequelae of meningitis are likely to hold sway in determining outcome.[19] Nonetheless, the implant surgeon should expect that ossification may be present and have an armamentarium of techniques available to deal with potentially unexpected findings.[56] Gantz and colleagues[57] described a more aggressive approach that optimized electrode insertion by creating a circumodiolar trough for the electrode using an extended transtympanic approach. The ear canal is divided and closed, and the ear canal skin, tympanic membrane, malleus, and incus are removed. The bony canal wall may be retained or taken down, but the prominence of the anterior bony external canal usually must be reduced to allow adequate visualization of the cochlear promontory. A cochleostomy is created, and a bridge of bone at the round window niche is preserved to help secure the electrode. The electrode array is then inserted beneath the bony bridge at the cochleostomy and into the lumen. Fibrous tissue is used to secure the electrode within the lumen. Additional strategies of implantation of the ossified basal turn involve opening the scala tympani.

Cochlear Malformations

Cochlear malformations pose potential risks to the surgical approach and opening of the inner ear. Up to 30 percent of children with congenital hearing loss have bony abnormalities of the labyrinth.[58] Cochlear malformation raises concerns about both surgical safety and postimplantation performance. Bony malformations of the cochlea have been associated with absence of the round and oval windows and with an aberrant course of the facial nerve. In addition, a thin cribriform area between the modiolus and a widened internal auditory canal is believed to be the route of cerebrospinal fluid leak when it occurs during surgery or spontaneously, as in the case of microscopic occult leak and recurrent meningitis.[59,60] An anomalous internal auditory canal may suggest absence of the auditory nerve, ordinarily a contraindication to implantation.[61,62] MRI may be used to delineate the

intracanalicular neural anatomy in detail.[63] Histopathologic studies of temporal bones with cochlear malformations reveal substantially diminished and, in one case, bilaterally absent SGC populations.[64,65,66,67] Even so, implantation of children with cochlear malformations can be achieved without surgical complications and can result in levels of performance comparable to patients with normal bony cochlear anatomy.[60,68,69,70,71,72,73,74] Modifications of conventional surgical implantation techniques are suggested and depend on a knowledge of the different types of malformations. Malformations based on embryogenesis are described by Jackler and colleagues[61] (Table F.1) as follows:

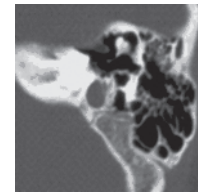
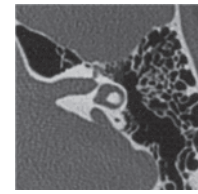
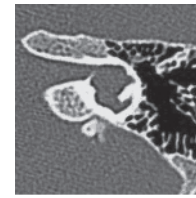
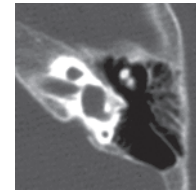
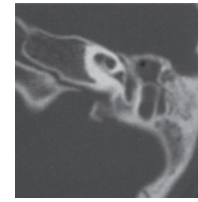
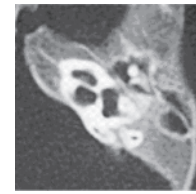
1. *Cochlear aplasia*: no cochlear development; these patients are not usually candidates for implantation, though Govaerts and colleagues[75] has suggested that patients with Type IIa aplasia may be implanted with reasonable benefit.
2. *Common cavity deformity*: combined cochlea and vestibule with no internal structure.
3. *Cochlear hypoplasia*: small cochlear bud.
4. *Incomplete partition*: classic Mondini malformation, with loss of interscalar septum between the middle and apical turns; cochlea are often smaller than normal.

Full or near-full electrode insertion can be achieved using routine implantation techniques in patients with incomplete partition (Mondini) deformity. A common cavity malformation is also likely to accommodate a multichannel electrode array, whereas the small size of the hypoplastic cochlea restricts the number of electrodes that can be positioned within the inner ear. Still, the two patients with cochlear hypoplasia in one series were able to use 10 electrodes each (Tucci and colleagues[60]). Because the electrodes may not be confined by scalar anatomy, electrode migration may occur, and individuals with cochlear malformations may require frequent reprogramming of the electrodes. Electrodes that are not intracochlear or that elicit facial nerve stimulation can be eliminated from the "map" as can electrodes that elicit facial nerve stimulation in implanted normal cochleae.

Abnormalities of the round window and facial nerve anatomy should be expected and the use of facial nerve monitoring is recommended. If the round window is absent, a cochleostomy should be placed according to the measurements described previously. The round window may be found in a position more posterior and superior than usual, consistent with the deformity of the cochlea. Malposition of the facial nerve may necessitate a modification of usual implantation techniques, and implantation through a vestibulotomy has been described. Facial nerve anomalies were found in 17

TABLE F.1 Malformations Based on Embryogenesis as Described by Jackler and Colleagues (Images courtesy of Johns Hopkins Medical Institutions)

Name (after Jackler et at.)[61]	Other Designations	Characteristic
Michel Deformity		Complete absence of vestibule and cochlea.
Cochlear Aplasia		Absent cochlea yet identifiable vestibule or semicircular canals.
Common Cavity		Defective fundus at lateral end of IAC. Risk of CSF gusher.
(No name distinguished by Jackler and colleagues)	Incomplete partition type 1,[10] Empty cochlea,[11] Pseudomondini,[12] Cystic cochleovestibular malformation	Cochlea is lacking the entire modiolus resulting in cystic appearance. Vestibule is similarly cystic.
Cochlear Hypoplasia	Cochleovestibular hypoplasia,[10] Dwarf cochlea[13]	Full vestibule-cochlear partition and normal number of turns, but abnormally small cochlea.
Incomplete Partition/ Mondini	Incomplete partition type 2[10]	Cochlea has 1.5 turns with basal modiolus. The apical turn has a cystic formation.

Anatomic Associations	Gestational Stage at Developmental Arrest	Axial CT Anatomy of Cochlea & Labyrinth
Often including absence of IAC.	Week 3	
Absence of promontorium distinguishes this from acquired ossified cochlea.	Late week 3	
IAC may be small, normal or large. Presence of neural tissue in the cavity is variable.	Week 4 (arrested at otocyst stage)	
Little more than a common cavity with a rudimentary partition.	Week 5	
	Approximately week 6	
Enlarged vestibular aqueduct. Spiral ganglia and nerve endings present (good implantation outcomes).	Week 7	

percent of children with malformations by Mylanus and colleagues,[76] though rates of up to 32 percent have been reported by Buchman and colleagues.[74] Particularly in cases where the nerve crosses the promontory, Hoffman and colleagues warn of facial nerve paralysis and suggest a sacrifice of the posterior canal wall for better visualization in difficult cases.[57] While Buchman and colleagues did not encounter either paresis or paralysis, they did note an association with adventitial facial nerve stimulation by the cochlear implant.

CSF leak is also a common hazard when implanting children with inner ear malformations. Rates of up to 50 percent have been reported.[70,71,72,73] Once the initial flow of CSF abates, soft tissue packing at the cochleostomy can readily fix the problem. However, in cases of persistent CSF leak, a lumbar spinal drain can be placed at the time of surgery and left in place for 3 to 4 days to allow the fibrous tissue packing in the cochleostomy to seal, preventing further leakage. Control of a CSF leak may also be accomplished by more extensive soft tissue packing of the middle ear space and Eustachian tube, with or without radical mastoidectomy and closure of the ear canal. An important, recently identified concern occurs when a CSF leak follows implantation of a malformed inner ear and results in early or delayed meningitis. Six of 26 cases of pediatric postimplantation meningitis found by Reefhuis and colleagues occurred in such instances.[91]

Intra-Operative Complications

Electrode Placement Problems

Electrode placement problems occurred in 0.58 percent of children.[34] Rather than its proper placement in the scala tympani, the electrode is occasionally misplaced into a hypotympanic air cell. Intraoperative radiography can help to guide the electrode to its precise location, and care should be taken to minimize the trauma to the membranous components of the cochlea during insertion.[77] If resistance is encountered, the electrode can be withdrawn slightly, rotated medially (counterclockwise for the right cochlea and clockwise for the left), and carefully advanced.[78,79,80] Because buckling of the implant can produce spiral ligament, basilar membrane, and localized neural injury, aggressive insertion attempts should be avoided.

Long-term complications involving the electrode (including migration) were found by Hoffman and Cohen in 1.31 percent of children.[121] However, Roland and colleagues have found no substantial migration over time in children.[44] Cohen and Hoffman suggest that packing the cochleostomy and facial recess with soft tissue may help to prevent migration.[81]

Facial Nerve Injury

Though rare, facial nerve injury is a serious potential complication of cochlear implantation. Studies focusing specifically on the incidence of injury in children are still lacking, but Hoffman and Cohen found a rate of facial nerve injury of 0.58 percent in 1,905 children.[110] House and Luxford[82] described eight cases, three of them pediatric, of facial paralysis or paresis that occurred after implantation. More recently, Fayad and colleagues[83] reviewed 705 implant recipients and found 4 to have post-operative facial nerve weakness. Of the 4, one was a 19-month-old child. Surgeons should be aware of aberrant positioning of the facial nerve in cases of cochlear malformation as well as the relatively small tolerances of the smaller corda-facial angle within the pediatric temporal bone.

In House and Luxford's eight cases, the most frequent mode of injury was the heat of the burr shaft rotating over the facial nerve in the facial recess. Copious irrigation during drilling, maintenance of a thin sheet of bone over the facial nerve in this location, and maintenance of an angle of drilling that keeps the burr shaft lateral and away from the floor of the facial recess are important in preventing injury. Intraoperative facial nerve monitoring may be helpful, but may not prevent injury from occurring. In Fayad and colleagues' review, the authors proposed neural edema in early onset palsy and acute nerve compromise or reactivation of herpes virus from surgical trauma in delayed onset palsy as possible mechanisms. Steroid treatment has been helpful in some cases of paresis.

INFECTIONS AND OTHER POST-OPERATIVE COMPLICATIONS

Otitis Media

One of the most common conditions affecting children, acute AOM carries small risk for the post-implantation patient. Infection can potentially spread along the electrode through the cochleostomy into the cochlea, particularly in a child who already has a pre-implantation history of AOM. Such a history, however, should not preclude or delay implantation as numerous studies have shown the decreased likelihood of the disease following surgery. House and colleagues[84] noted that with (1) the natural decline in cases with age, (2) effective antibiotic, or (3) mastoidectomy treatment, children often develop fewer instances of AOM than prior to implantation. Similarly, Luntz and colleagues[85] reported that neither the prevalence nor the severity of AOM increased with implantation, although children with a history of AOM did show a higher risk of developing post-implantation infection. Their data showed a decrease in AOM from 74 percent pre-operatively to 16 percent post-operatively, with all post-

operative cases treated successfully and without any complications. Fayad and colleagues[86] also found a significant decrease in cases of otitis media after implantation, both in children with and without a history of bilateral myringotomy and tubes, and Kempf and colleagues[87] found only a 5.6 percent post-implantation rate of AOM.

Ideally, AOM should be controlled before surgery. Children with pre-implantation histories of AOM should be treated prior to the operation with adenoidectomy or ventilation tubes. If AOM develops during either the peri-operative or post-operative period, Kempf and colleagues recommend prompt treatment with intravenous antibiotics and mastoidectomy if necessary. In cases of severe infection, removal of the device is possible with future reimplantation as an option.[87] Papsin and colleagues[88] suggest that effusion at the time of implantation does not pose peri-operative difficulties; they recommend peri-implant myringotomy tubes with peri-implant antibiotics to protect against peri-operative infections.

Device Infection

Foreign objects within the inner ear are potential breeding grounds for infection and can lead to life-threatening episodes of meningitis. Nadol and Eddington's study of 21 temporal bones found that late hematogenous contamination and colonization of the device are likely mechanisms for the pathogenesis of meningitis.[89] Such infections of the device can be difficult to treat as biofilms create a barrier between the bacteria and antibiotics. Removal of the implant may be necessary, if incision, drainage, and intravenous antibiotics fail. The possibility of bacterial biofilm development on the surface of the cochlear implant is increasingly recognized in cases of persistent and recurrent abscess or granulation tissue formation.[90] This observation is critical as biofilms confer substantial bacterial resistance to host defenses. Such observations carry implications for device design. They suggest, for example, that surface openings to accommodate retention magnets and electronic grounding should be sealed and offer no confines for contaminants to be isolated from immuno-surveillance.

Post-Implantation Meningitis

In 2002, an alarming increase in the number of post-implantation meningitis cases noted anecdotally and through reports to the FDA prompted health care agency investigations in both Europe and North America.[91] Initial reports suggested a higher risk of meningitis in patients implanted with a particular device design and particularly when placed with an intracochlear shim (electrode positioner), and the manufacturer ultimately recalled unimplanted devices utilizing the positioner in July 2002. The level

of risk did not suggest the need for positioner removal unless repeated infections of any kind are encountered. Since then, continued studies have revealed a higher risk for the disease in patients with all cochlear implants compared to the general population. Children appear to be particularly affected: of the 52 cases originally reported by the FDA, 33 (63 percent) were under the age of 7.

Reefhuis and colleagues[91] conducted a study of 4,264 children implanted between 1997 and 2002 and found 29 cases of bacterial meningitis in 26 of the children. This rate of meningitis (caused by *Streptococcus pneumoniae*) was 30 times the incidence in the general population. While the use of a positioner increased the likelihood for contracting meningitis, even children who were implanted without a positioner had rates of meningitis 16 times higher than the general population. Case-control analysis found the following risk factors: a history of placement of a ventriculoperitoneal (CSF) shunt, a history of otitis media prior to implantation, the presence of inner-ear malformations with CSF leak and CSF leaks alone, the use of a positioner, incomplete insertion of the electrode, signs of middle-ear inflammation at the time of implantation, and exposure to smoking in the household. While the incidence of meningitis decreased considerably after the peri-operative period, cases still appeared even 2 years after implantation.

The design of the study conducted by Reefhuis and colleagues, as noted by the authors, did not permit the comparison of meningitis risk between deaf children with and without a cochlear implant. That is, there is no comprehensive epidemiologic analysis of the risk of meningitis in deaf children but no cochlear implants. It is biologically plausible that greater risk of meningitis exists in deaf children in general given high levels of associations of deafness with skull base anomalies that predispose them to the disease. It is also possible that any surgical implant placed in or near the skull base of toddlers and young children (e.g., CSF shunts) does indeed carry a prolonged risk of meningitis.

Callanan and Poje[92] similarly found an association between meningitis and the use of a positioner and congenital malformations. Another risk factor may be hyperbaric oxygen therapy; in children with cerebral palsy it was associated with middle ear complications. Of the congenital malformations, Mondini dysplasia has generated the most attention for its predisposition to CSF leaks. Page and Eby[93] reported a case of CSF otorhinorrhea and meningitis 2 years post-implantation in a child with Mondini dysplasia and suggested careful seals of the cochleostomy to prevent CSF leakage. Suzuki and colleagues[94] also reported a case of fatal meningitis with chronic otitis media and bilateral CSF leaks in a 6-year-old boy 2 years following implantation. However, it should be remembered, as O'Donoghue and colleagues[95] point out, profoundly deaf patients who are likely to undergo

cochlear implantation may already be at increased risk for meningitis particularly in the context of a CT-evident cochlear anomaly.

Mechanisms for post-implantation meningitis for children with implants have been proposed by Cohen and colleagues.[96] Infections may result from the direct spread of otitis media into the scala tympani, either at the time of surgery in immediate cases or some time following surgery in delayed cases. Also, the trauma caused by surgery may activate latent colonies of pneumococci and the drilling of the well for device placement may allow exposure and subsequent translocation of postsurgical, neovascularized dura. Finally, hematogenous spread of infection or factors relating to the surface of the device itself may cause meningitis.

Given the dangers posed by meningitis (mortality rates range from 15 to 60 percent), the Center for Disease Control and Prevention recommends pneumococcal vaccination for all cochlear implant recipients following age-appropriate schedules.[97] These vaccinations should be completed 2 or more weeks prior to surgery. Reefhuis and colleagues further suggest careful monitoring for signs and symptoms of meningitis in the post-operative period, timely diagnosis and treatment of acute otitis media to prevent the spread of infection, and awareness of any inner ear malformations or other surgical findings that may predispose the child to meningitis.[91] If meningitis develops, however, consideration of removal of the implant is individualized given the risk for surgical complications that might exacerbate the conditions leading to meningitis.

Tinnitus and Vestibular and Balance Function

While no studies have tracked tinnitus in pediatric cochlear implant recipients, many have established an association between cochlear implantation and a reduction in tinnitus.[98,99,100] Ruckenstein and colleagues' review of 38 adult patients with pre-implantation tinnitus found that 92 percent had statistically and clinically significant reductions in their symptoms following implantation.[101] Miyamoto and Bichey's review of recent literature confirmed these results, but noted that the prevalence of tinnitus in pre-operative implant recipients was extremely high at 80 to 90 percent.[102] Children are generally believed to have a lower prevalence of tinnitus, yet how they detect and report symptoms remains unclear. Still, Aschendorff and colleagues found a similar reduction in tinnitus following implantation in adolescent patients.[103] Further studies are necessary to clarify tinnitus in children receiving implants.

Similarly, research on vertigo in post-implantation children is scarce. In adult populations, vertigo is a common complaint following surgery, with the vast majority of patients noting resolution of active vertigo within 72 hours of surgery. Caloric testing on cochlear implant recipients showed that

while implantation did not abolish vestibular function, temporary disturbances were seen in 20 percent of patients,[104] thus yielding the possibility of post-implantation disequilibrium and vertigo. During the first week after surgery, patients often experience some degree of disequilibrium and unsteadiness. True vertigo that persists in the post-operative phase is rare.[105] Extended periods of disequilibrium are also rare, but, when present, are treatable with exercise regimens designed to elicit central compensatory mechanisms. Kubo and colleagues[106] reported a 49 percent rate of vertigo in 94 adult implant recipients and similar results were found by Ito.[107] Fina and colleagues[108] found a lower rate of 39 percent while Steenerson and Gary[109] reported that up to 75 percent of adults with implants experienced vertigo or imbalance. Most of Fina and colleagues' 75 patients experienced delayed, episodic vertigo and had a history of pre-operative dizziness. Like tinnitus, vertigo is more likely to affect older populations; the incidence in children is still unknown though clinical observations (e.g., rare instances of obvious nystagmus) suggest that it is uncommon.

Scalp Flap Complications

The most frequently reported major and minor complications are related to the incision and postauricular flap design. Problems range in severity from minor wound dehiscences or infections to major loss of tissue necessitating removal of the device. In a study of 3,064 adults and 1,905 children who received implants, Hoffman and Cohen[110] found the overall rate of flap complications to be 4.5 percent. Flap necrosis occurred in 0.37 percent of children while flap infection was found in 0.73 percent of children. Fifty-five percent of all flap complications were considered major and required follow-up surgery.

Many implant surgeons have thus emphasized the importance of good flap design and technical skill to avoid these complications. Ideally, the flap should have adequate blood supply and venous drainage, allow enough exposure of the operative site with sufficient coverage of the device, and be carefully closed in layers without tension. Because it is associated with complications,[111] a C-shaped incision is contraindicated when there is a previous post-auricular incision.[112] Inverted U- and J-shaped flaps take advantage of the posterior arterial supply. Because these flaps have the disadvantage of crossing the electrode lead as it enters the mastoid cavity, it is necessary to create an anteriorly based musculofacial flap (i.e., Palva flap) under the scalp to ensure electrode coverage.

Other suggestions have included straight, post-auricular incisions. Gibson and colleagues[113] developed a 7 cm vertical entry route found to minimize scalp infection and device extrusion in 20 adults and 32 children. O'Donoghue and Nikolopoulos's minimal access surgical route is a 3 cm

oblique incision.[46] Of their 23 pediatric cases, no major complications occurred, and only 3 instances of wound edema were encountered.

As Cohen and Hoffman warn,[114] flaps that are too thick will impede the transmission of electrical signals, whereas flaps that are too thin will erode under the magnetic pressure. Careful handling of the flap, with proper moisture and hemostasis, and suture placement away from the surface of the implant are especially important. Signs of flap infection or necrosis should be immediately treated with topical or oral antibiotics to avoid removal of the device. More persistent cases of infection should be treated with intravenous antibiotics and surgery if necessary. Extrusion of the device can result from local flap necrosis, which can be managed by rotation of the device under an extended flap, usually to a more superior location where intact skin covers the device.[115,116]

Facial Nerve Stimulation

With initial use of the cochlear implant, current flow through the facial nerve may cause undesirable stimulation. Kempf and colleagues found 11 cases out of 66 children with such a problem.[87] Facial nerve stimulation is usually easily solved by changing stimulation patterns and eliminating offending electrodes that inject errant electrical signals. In rare cases the stimulation persists, though, and the device may not be able to be used by the patient.

Histopathology of Implanted Temporal Bones

The histologic results of cochlear implantation have been well studied.[117,118,119,120] Potential histopathologic findings can be divided into surgical and device-related injuries. Surgical trauma may include fractures of the osseous spiral lamina, perforation of the basilar membrane, and tears of the spiral ligament. Cochlear fibrosis and neoossification are common findings in these studies. In general, traumatic changes appear to be limited to the most basal portions of the cochlea and are unlikely to exert significant negative effects on implant performance. Reactions to extended electrical stimulation (e.g., electrochemical tissue damage, neural degeneration) by current implants appear to be modest. Foreign body reactions and infections that extend along the implant array to involve membranous elements of the cochlea are likely to induce sensorineural degeneration. However, well-documented cases of such occurrences are lacking.

Findings of localized cochlear trauma after cochlear implantation have led to concerns that these traumatic injuries might result in associated SGC degeneration. Although two studies of temporal bone histopathology in individual patients with a unilateral cochlear implant report a decrease in

the normal SGC population ipsilateral to the implant (Zappia and colleagues),[119] other studies in chronically implanted animals[121,122] and humans[123,124,125] showed no differences in SGC populations between the implanted and unimplanted ears. It is likely that many factors influence neuron survival, as evidenced by histopathologic studies, including previous pathology (which may vary between the two ears) and the amount of time between implantation (with possible end organ damage) and the time of death. Because the temporal association between SGC degeneration and end organ damage has not been clearly established for humans, histopathologic findings from implanted temporal bones are not always clearly interpretable. Although the duration of implant stimulation in the Linthicum study ranged from 1 to 14 years, Nadol's report was limited to the study of one set of temporal bones from a patient implanted 10 weeks before death.[120] Animal studies have shown that the reintroduction of electrical activity through a cochlear implant may prevent degenerative changes in the central auditory system.[126,127]

DEVICE FAILURE

The cochlear implant system may demonstrate failure either as a result of complete loss of electrical connectivity or current shunting/shorting. Either the internal, implanted device or the external processor may be affected.

Device failure as a result of loss of electrical function in the external processor commonly produces a sudden loss of function and, therefore, hearing. Intermittency and rarely popping sensations occur before processor failure. Processor functionality may be lost with direct trauma to the unit, exposure to water, and, most frequently, normal wear and tear of connecting lead-wires linking the processor unit with the magnetically-retained antenna that relays information to the internal device. Manufacturers' inserts and websites and cochlear implant clinics offer readily available troubleshooting guides to either correct the problem with the external unit or prompt processor replacement.

Although much less prevalent, device failure as a result of loss of electrical function in the internal device is of considerably greater concern. An internal device failure typically presents as either an immediate cessation of function or intermittency that is associated with reduced quality of sound and diminishing periods of function over days to weeks. Reports of painful stimulation have been noted, but are fortunately rare.

As all devices are current-limited at levels well below the threshold for tissue injury, symptoms of painful stimulation probably reflect adventitial stimulation of middle ear sensory nerves as a result of current shunting. However, hermeticity failures may be associated with DC leakage as suggested by failure analysis of explanted devices. The presence of moisture in

the implant case can result in dendrite formation and short circuiting of the safety mechanisms (e.g., capacitors), which are designed to prevent neural overstimulation. To date, there are no clear case reports of DC leakage or shorting of RF energy to the electrode resulting in permanent neurological damage, but such injury may be possible and the likely clinical manifestations would be pain. This would presumably prompt adults and older children to immediately cease use of the device, which provides an additional safety net against permanent neurological damage. Unfortunately, infants and younger children would not necessarily be able to remove the noxious stimuli, and there could be a delay in recognition of the problem by parents and caregivers, leaving this younger population more vulnerable to injury. Such possibilities should be made clear to clinical teams who provide services to families with infants and young children with cochlear implants.

Diagnosis of the mode of failure of an internal device is hampered when the implant lacks telemetry to enable electrical assessment of all contained circuits. When telemetry is available, removing select channels from the "map" of stimulated circuits may allow for continued function. In the absence of telemetry, revision surgery may be the only alternative when the clinical team deems the implant nonfunctional.

Explanted devices are sent to the manufacturer for bench assessment of circuit integrity. Formal data on analyses of explanted devices have yet to be reported. However, for the purposes of this review the senior author interviewed manufacturers' engineers and found general trends in patterns of failure across manufacturers. Of devices with a recognizable fault, the general pattern of failure mode occurs with a relative incidence of

- Hermeticity or moisture: 75 percent (0.75 percent total)
- Electronic / Hybrid failure: 16 percent (0.16 percent total)
- Electrode / Connecting lead: 9 percent (0.09 percent total)

As a whole, cochlear implants have maintained a historical reliability of 99 percent at 1 year, meaning that 99 percent of devices remain working at the 1 year interval. Reliability data have only recently been disclosed for public review by one of the implant manufacturers. It should be noted, however, that the integrity of the data on reliability is subject to under- or misreporting due to a lack of agreement on what constitutes a "device failure" and the challenges associated with ongoing communications an estimated 1,000 cochlear implant centers internationally.

Notwithstanding these uncertainties, reported trends suggest that device reliability has improved over the past 30 years.[128] For example, the failure rate for the third generation Cochlear Corporation device released in

2001 (0.3 percent/year) is approximately one-third of that associated with its first generation device used from 1985 to 1998 (0.8 percent).

The need for revision surgery to replace the internal device has motivated scrutiny of potential sources of manufacturing and material defects. In the past year, FDA has examined manufacturing processes at all three major manufacturers with public disclosure of concerns relating to two of the three (see www.fda.gov/foi/warning_letters/g5089d.htm and www.fda.gov/foi/warning_letters/g5265d.htm).

Although cochlear implant technology has improved significantly over the past few years, children remain at an unspecified level of increased risk for device failure given higher activity levels and predisposition to direct trauma.[129] A trend toward device failures with direct device impact, particularly in toddlers and very young children, associated with a particular grade of ceramic casing used in Clarion devices manufactured in the mid-1990s led to a change in the grade of the ceramic used. Subsequently, this manufacturer has adopted a titanium case embedded in soft, solid silastic.

Device failure is the most common indication for revision surgery and cochlear reimplantation. "Upgrades" to more advanced models are rarely indicated as the level of performance enhancement achievable is subject to individual case consideration. Infection and flap breakdown require reimplantation less frequently.[130]

Luetje and Jackson[131] reported a 9 percent rate of device failure in a review of 55 children, which matched results found by Parisier and colleagues.[132] The most common failures include fracture of the central pin feed-through for the antenna coil, damaged integrated circuits in the internal receiver from electrostatic discharges (occasionally associated with contact and friction with playground-grade polyethylene), damaged electrodes exiting from the internal receiver, capacitor failure, and electrode-array damage.

Detection of device failure is imperative in the implanted child. Parisier and colleagues' analysis identified four major risk factors that point to failure: fluctuations in threshold and comfort levels of nine units for more than six electrodes, performance incompatible with age and duration of deafness, complaints of extraneous noises and intermittent shocks, and a high number of external equipment changes.[131] Tests on the device showing an absence of recorded output, abnormal pulse configuration, or lack of amplitude increase in response to increased stimulation can verify failure.

Prevention of device failure in children begins with proper securing of the implant, particularly the connecting lead between the receiver/stimulator and the electrode array, which is vulnerable to shearing. The device should be embedded in a well drilled in bone and fixed with permanent suture material. While the evolution of implant design has certainly decreased the

rate of device failure, these precautions may help to shield the device from traumatic events.

Should device failure occur, though, reimplantation is the most viable solution. The most common challenges encountered include fibrosis and ossification of the cochleostomy, as well as skin flap breakdown and CSF leakage.[133,134,135,136] Theoretical concerns relate to hair cell and spiral ganglion cell damage from further surgical trauma, though clinical evidence of trauma with reimplantation is lacking. Special attention should be paid to the skin flap given the frequency of atrophy following primary implantation and removal of bone at the cochleostomy may be necessary. Alexiades and colleagues suggest that if significant scar tissue surrounds the lead wire, facial recess, or cochleostomy, the lead wire can be severed away from the electrode array to ease removal of the old device and insertion of a replacement (although this procedure may hamper the subsequent device analysis discussed above).[130]

Despite technical challenges, insertion of all electrodes is usually possible, as Parisier and colleagues found.[136] Balkany and colleagues'[134] review of 16 subjects, 11 of them pediatric, found insertion length to be greater than in the primary surgery. Only Miyamoto and colleagues found a small but statistically significant decrease in reimplant insertion and the number of active channels.[133]

Performance following reimplantation is generally promising. Parisier and colleagues' review of 25 children found that speech perception abilities had remained the same or had improved overall.[136] In particular, these children demonstrated continued improvement in open-set speech recognition. Similar reimplantation results were found in Alexiades and colleagues' review of 20 children[135] and in Haensel and colleagues' review[137] of 11 children. If the technical challenges of reimplantation surgery can be overcome, children may benefit greatly from the revision with little risk of compromised performance.

RISKS FOR POOR COMMUNICATION OUTCOMES

Cochlear implants can have impressive effects on a child's language abilities, yet outcomes remain variable across the pediatric population. Numerous studies have thus attempted to identify predictors determining post-implantation communication. So far, relevant factors are age at onset of deafness, age at implantation, length of implant use, amount of residual hearing, duration of deafness, educational mode and resources, and psychosocial elements.

A clear factor seems to be the age at implantation: children appear to perform better when implanted at earlier stages.[138,139,140,141] On IT-MAIS testing, Robbins and colleagues found that children implanted under the

age of 19 months demonstrated faster progress and higher scores than those implanted between the ages of 2 and 3.[140] As Geers[142] found, though, this age advantage disappears after 2 years, implying a critical period of development within the first 2 years of life. At older ages, then, other factors begin to affect implant performance. In particular, duration of deafness, pre-operative open-set score, and equivalent language age were found by Dowell and colleagues[143] to explain a large percentage of the variance in speech perception scores of children implanted between the ages of 8 and 18. Children with an earlier age at onset of deafness and with greater durations of deafness tend to have poorer outcomes.[144]

At the same time, educational resources must be attuned to the child with a cochlear implant in order to achieve optimal benefit. Classrooms emphasizing total communication rather than oral communication have been found to limit the speech intelligibility abilities and phonological processing skills of children.[145,146] Placement in oral communication settings have allowed a greater number of implanted children to eventually join mainstream classrooms in which speech intelligibility scores are further enhanced through interaction with hearing peers. However, oral communication is not enough to ensure the proper progression of the child through schooling. Cooperation between parents, school administrators, teachers, and speech specialists is also vital to the success of the child. Luetje and Jackson[130] noted that insufficient funds for special education programs with trained speech and language professionals and adversarial relationships between all parties involved are detrimental to the child's progress. These adverse circumstances are made worse in regions of the country where services to deaf children are scarce.

The child's family unit is another integral part of the rehabilitation process. Nikolopoulos and colleagues[147] found family structure and support to be significant predictors of outcome. Without full investment of the family in the child's learning and development maximum benefit from the implant may never be reached. Unfortunately, many families are under considerable stress due to their children's condition. Spahn and colleagues[148] found that a quarter of parents of cochlear implant recipients suffer from high psychic stress, with 18 percent needing psychosocial support. Awareness and prompt treatment of these issues may prevent further delays in the child's progress, although the exact effects of parental stress on child development with an implant remain unclear.

Overcoming these obstacles can help the child achieve successful outcomes with a cochlear implant. The gains that can be made through implantation are certainly impressive; not only have implanted children shown remarkable improvements in language ability, educational attainment, and social integration, but they have also proven the procedure to be economically beneficial. Cost–utility analyses by O'Neill and colleagues[149] and

Cheng and colleagues[150] have demonstrated considerable quality of life gains at reasonable costs, particularly when compared to other health care interventions.

It is clear, however, that early cochlear implantation does not provide a "mainstream" educational and psychosocial developmental opportunity for all childhood recipients. The extent to which device-specific factors may impose constraints in developmental learning will require longitudinal, multivariate analysis. If device-specific factors predicting poor long-term performance were identified, their occurrence would have to be considered in the context of a device-related complication.

TRACKING COMPLICATIONS ASSOCIATED WITH COCHLEAR IMPLANTS IN CHILDREN

The above survey of the peer-reviewed literature presents only the range of *reported* complications associated with cochlear implantation in children. Substantial uncertainty remains regarding the precise rates of complications, and there is insufficient epidemiologic data with which to better understand potential source(s) of adverse outcomes that may be associated with cochlear implants in children.

The importance of tracking complications associated with cochlear implants in children is underscored by the enthusiasm associated with the application of advancing technologies to a significant disability. For example, microprocessing technology has propelled communication technologies of increasing sophistication for the general population. Advances in information processing, when incorporated into cochlear implants, are commonly perceived as naturally contributing to an improved speech code and an improved outcome for deaf children. Indeed, virtually all introductions of newer models of speech processors for cochlear implants have entailed higher rates of information transfer. Faster processing capabilities result from the integration of literally more millions of transistors into progressively smaller body- and ear-worn speech processors. As ever larger numbers of components are fit onto microchips then, a move to new implant designs that facilitate the delivery of more sophisticated codes has followed in at least seven instances. Such circumstances, however, risk a potentially hazardous scenario wherein technology drives the development of devices for biologic application in the absence of long-term, quality data that track *in vivo* effects.

The field of pediatric cochlear implantation has generally advanced only after periods of months to years of observation of successful experience with newly designed devices in adults. This cautious approach may still fail to ensure safety for childhood applications. In fact, observations emanating from the identification of the risk posed by cochlear implants for

meningitis in children in 2002 indicated that complications of particular concern to children can arise and that trends can go undetected for years.[91] It also appears that complications unique to children can arise after highly variable periods of time following surgical implantation, thus necessitating follow-up for indefinite periods of time. For example, the current database on pediatric cochlear implant users is not sufficiently robust to enable a formal determination of meningitis risk going forward as new implant types are introduced. These observations emphasize the need for mandatory reporting requirements and better quality reporting to facilitate the early detection of health-related complications in cochlear implant users.

Manufacturer-based reports on cochlear implant complications are often supplied in direct correspondences and in newsletters to clinicians. However, such reports are often provided in the context of marketing device durability, suggesting that some datasets may go unreported in manufacturer communications. In addition to reports, independently-tracked data are needed to provide a more useful profile. The above summary of pediatric cochlear implant complications from the peer-reviewed literature represents the best efforts of clinicians to gather information about complications from case series, and manufacturer and FDA datasets.

The cornerstone for FDA's postmarket surveillance of medical devices is the information provided by both voluntary and mandatory device-related adverse event reports to the Agency. (For additional description, see Chapters 3 and 4 of the Institute of Medicine report in which this appendix appears.[151]) Voluntary reporting to FDA began in 1973, and the current MedWatch Program, created in 1993, provides a mechanism for consumers and health care professionals to voluntarily report problems with medical devices by phone, mail, or online completion of an adverse event form. More recently, FDA has developed partnerships with major health care organizations in the United States to promote reporting adverse events through this program, particularly those of a serious nature.

In 1984 FDA implemented the MDR (Medical Device Reporting) regulation, which requires manufacturers and importers to report all device-related deaths, serious injuries, and malfunctions to the Agency. Additionally, under the Safe Medical Devices Act of 1990 and other subsequent legislation, user facilities (e.g., hospitals, nursing homes) are also now required to report: (1) device-related deaths to both FDA and the manufacturer, (2) device-related serious injuries to the manufacturer (or to the FDA if the manufacturer is unknown), and (3) an annual summary report of deaths and serious injuries to FDA. Although legal enforcement of these mandatory reporting requirements is possible and FDA does inspect manufacturer facilities for compliance with adverse event record keeping and reporting, FDA has relied on the goodwill and cooperation of manufacturers and user facilities to ensure compliance with the regulation and charac-

terization of the potential sources of the complication. Of note, individual health professionals are not required to report events. This is not an insignificant source of cochlear implant surgeries for children in the United States.

The specific requirements for device-related adverse event reporting are outlined in federal regulation at 21 CFR 803. Briefly, manufacturers are required to report deaths, serious injuries, and malfunctions to FDA within 30 calendar days. When an adverse event requires remedial action to prevent an unreasonable risk to public health (or when another event designated by FDA occurs), manufacturers must report the event to the agency within 5 work days. User facilities must report deaths and serious injuries within 10 work days, and must also file an annual report to FDA of deaths and serious injuries.

In actual practice, reporting from user facilities has been low (less than 3 percent of adverse event reports to the Agency in 1999). Recognizing the value and importance of adverse event reporting experience from user facilities in postmarket surveillance, Congress mandated, under the FDA Modernization Act of 1997, that a focused network of well-trained and highly motivated user facilities be created to enhance detection of emerging device problems and to act as a two-way communication channel between FDA and the clinical community. This network, known as the Medical Product Surveillance Network (MedSun), is currently under development and will consist of at least 250 hospitals and approximately 50 nursing homes. MedSun aims to achieve a reasonably representative sample of user facilities (primarily hospitals) that may allow for national estimates on certain device issues in the future. This network could eventually provide a consistent, reliable source of postmarket clinical experience in children with cochlear implants.

Adverse events, whether from voluntary or mandatory reports, are entered into the FDA's Manufacturer User Facility and Distributor Experience (MAUDE) database. MAUDE contains reports from user facilities since 1991, voluntary reports to the Agency since June 1993, distributor (e.g., importers) reports since 1993, and manufacturer reports since August 1996. Within FDA's Center for Devices and Radiological Health (CDRH), the Office of Surveillance and Biometrics routinely monitors and analyzes incoming reports to detect signals of significant postmarket safety and effectiveness concerns. Information from these reports is disclosed to the public and is available on the web in the MAUDE database (www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfMAUDE/search.CFM).

An informal analysis of MAUDE suggests that in its current state, the database lacks sensitivity for complications that can be managed medically or are related to surgical technique; such complications would seem to be unlikely to be reported to FDA.[152] The MAUDE dataset is intended for

serious complications that result from errors in the use of a device or device malfunction. Even for complications such as device failure, however, there is often an absence of data, such as device lifespan prior to failure and uniform terminology regarding failure modes (e.g., hermeticity breach, electrode wire breakage). These data would likely prove invaluable in analyzing trends. Information such as patient age, date of implant, surgical approach and relevant surgical anatomy, prior surgeries, and characteristics of the implant center are often not included in the MAUDE reports. To be effective, the MAUDE database will need to be structured to provide detailed information on individual medical devices. This will require *a priori* form design that offers heightened sensitivity and specificity in characterizing device-related complications. Form 3500A (www.fda.gov/medwatch/safety/3500a.pdf) is quite detailed. One problem, however, is that it often is not filled out completely by the manufacturer or user facility—due either to lack of information or other issues.

For cochlear implants, the MAUDE database might be strengthened with regular, timely provision to FDA of manufacturer and distributor data on the number of devices implanted (i.e., denominator data) and trends with respect to recipient demographics could construct a crucial background of device distributional patterns. For example, when cases of meningitis were reported at an alarming rate in 2002, it was completely unclear as to whether the higher incidence of this complication may have coincided with clinical trends of implantation of younger ages. Epoch analyses are likely to be extremely instructive in determining the source(s) of device-related complications. Such analyses would be afforded with updated, high-quality epidemiologic datasets.

It is apparent, however, that the establishment of a uniform, comprehensive, and up-to-date national database of device-related complications faces monumental obstacles. For example, manufacturers may be reluctant to publicly provide data on devices implanted for defined time periods (i.e., denominator data) because this would reveal potentially sensitive information regarding market share. Another very practical issue that hampers ongoing tracking is that families of children with cochlear implants are young and highly likely to change their address within any 5 to 10 year period. A recent experience is instructive. The Advanced Bionics Corporation made a concerted effort to contact every user of its cochlear implant systems (n = ~12,000) in association with the meningitis reports of 2002 with direct, registered mail. Despite using updated address information based on warranty registration, the corporation was able to contact less than 90 percent of users at a cost of over $300,000. While the inability to contact more than 10 percent of users is less than ideal, it is higher than might be expected. Because children and most adults with cochlear implants require regular follow-up, their regular contact with clinics may

promote high rates of information updating and thus relatively high access when compared with patient groups using other implants.

The above experience underscores that some cochlear implant device users and their families appear to go without close, regular follow-up by a medical facility. Moreover, address changes are not always available from manufacturer and patient records. This experience, however, does suggest that ongoing manufacturer to FDA communications and warranty-related contact information can provide an important means of informing trends in device-related complications. This would seem to be particularly important with respect to childhood recipients. The establishment of a dedicated, pediatric database that draws on multiple sources of information deserves further consideration.

In addition to adverse event reporting requirements, FDA may also mandate that manufacturers perform postmarket studies either as a condition of the original FDA approval or under the FDA Modernization Act (Section 522) authorities. High-risk implantable devices (e.g., cochlear implants) require FDA approval of a premarket approval application (PMA) prior to marketing to ensure their safety and effectiveness. Along with the specific adverse event reporting requirements listed in the PMA Conditions of Approval, the Agency may also include an additional "condition" for the manufacturer to address specific safety and/or effectiveness issues through a postapproval study. For example, cochlear implant manufacturers have often been required to collect additional long-term clinical data on pediatric patients to demonstrate safety and effectiveness of the device in this population. Alternatively, the Agency may impose postmarket study requirements for certain devices under Section 522 of the Federal Food, Drug, and Cosmetic Act. This authority allows FDA, under its discretion and for good reason, to order manufacturers to conduct postmarket surveillance on Class II or III devices that are implanted in the human body for more than 1 year, life-sustaining or life-supporting devices used outside of a device user facility, or devices the failure of which would be reasonably likely to have serious adverse health consequences. These studies are generally reserved for potential device failure situations that would be reasonably likely to have serious adverse health consequences. Under these circumstances, FDA can require prospective surveillance period of up to 36 months.

Reviews of major complications associated with implantable devices suggest that two approaches to monitoring device safety might be expanded: (1) the role of clinicians in reporting potential device-related complications, and (2) the visibility of a centralized data coordination center. Health care providers are the likely contact for virtually all complications related to device use. The responsibility of clinicians to report major device complications is in the interest of the public's health and should be underscored in licensing requirements. Successful completion of web-based training mod-

ules used recently to inform clinicians of new Health Insurance Portability and Accountability Act and Effort-Reporting regulations could be used to develop new approaches to device-use surveillance and may be held as a requirement for licensure. Such training should also promote complete understanding of mechanisms of reporting to a data coordination center that is singularly recognized as *the* site for the accrual of data on device complications.

REFERENCES

[1]Reis R. Prevalence and characteristics of persons with hearing trouble: United States, 1990–1991. National Center for Health Statistics. *Vital Health Stat 10* 1994:1–134.

[2]Blanchfield B, Dunbar J, Feldman J, Gardner E. *The Severely to Profoundly Hearing Impaired Population in the United States: Prevalence and Demographics*. Bethesda, Md: Project HOPE Center for Health Affairs, 1999.

[3]Berliner K, Eisenberg L. Methods and issues in the cochlear implantation of children: an overview. *Ear Hear* 1985;6:(Suppl 3) 6S–13S.

[4]Ling D. *Foundations of Spoken Language for Hearing Impaired Children*. Washington, DC: Alexander Graham Bell Assoc for the Deaf, 1989.

[5]Parisier SC, Chute PM, Popp AL, et al. Surgical techniques for cochlear implantation in the very young child. *Otolaryngol Head Neck Surg* 1997;117:248–254.

[6]Waltzman SB, Cohen NL. Cochlear implantation in children younger than 2 years old. *Am J Otolaryngol* 1998;19:158–162.

[7]Lenarz T. Cochlear implantation in children under the age of two years. *Adv Otorhinolaryngol* 1997;52:204–210.

[8]Novak MA, Firszt JB, Rotz LA, et al. Cochlear implants in infants and toddlers. *Ann Otol Rhinol Laryngol Suppl* 2000;185:46–49.

[9]Hehar SS, Nikolopoulos TP, Gibbin KP, et al. Surgery and functional outcomes in deaf children receiving cochlear implants before age 2 years. *Arch Otolaryngol Head Neck Surg* 2002;128:11–14.

[10]Zwolan TA, Ashbaugh CM, Alarfaj A, et al. Pediatric cochlear implant patient performance as a function of age at implantation. *Otol Neurotol* 2004;25:112–120.

[11]Robbins AM, Koch DB, Osberger MJ, et al. Effect of age at cochlear implantation on auditory skill development in infants and toddlers. *Arch Otolaryngol Head Neck Surg* 2004; 130:570–574.

[12]Schauwers K, Gillis S, Daemers K, et al. Cochlear implantation between 5 and 20 months of age: the onset of babbling and the audiologic outcome. *Otol Neurotol* 2004;25:263–270.

[13]Govaerts PJ, De Beukelaer C, Daemers K, et al. Outcome of cochlear implantation at different ages from 0 to 6 years. *Otol Neurotol* 2002;23:885–890.

[14]Young NM. Infant cochlear implantation and anesthetic risk. *Ann Otol Rhinol Laryngol Suppl* 2002;189:49–51.

[15]Waltzman SB, Scalchunes V, Cohen NL. Performance of multiply handicapped children using cochlear implants. *Am J Otol* 2000;21:349–335.

[16]Hamzavi J, Baumgartner WD, Egelierler B, et al. Follow up of cochlear implanted handicapped children. *Int J Ped Otorhinolaryngol* 2000;56:169–174.

[17]Fukuda S, Fukushima K, Maeda Y, et al. Language development of a multiply handicapped child after cochlear implantation. *Int J Ped Otorhinolaryngol* 2003;67:627–633.

[18]Donaldson AI, Heavner KS, Zwolan TA. Measuring progress in children with autism spectrum disorder who have cochlear implants. *Arch Otolaryngol Head Neck Surg* 2004;130: 666–671.

[19]Francis HW, Pulsifer MB, Chinnici J, et al. Effects of central nervous system residua on cochlear implant results in children deafened by meningitis. *Arch Otolaryngol Head Neck Surg* 2004;130:604–611.

[20]Luntz M, Teszler CB, Shpak T, et al. Cochlear implantation in healthy and otitis–prone children: a prospective study. *Laryngoscope* 2001;111:1614–1618.

[21]Luntz M, Teszler CB, Shpak T. Cochlear implantation in children with otitis media: second stage of a long-term prospective study. *Int J Pediatr Otorhinolaryngol* 2004;68:273–280.

[22]Dettman SJ, D'Costa, WA, Dowell RC, et al. Cochlear implants for children with significant residual hearing. *Arch Otolaryngol Head Neck Surg* 2004;130:612–618.

[23]Mecklenburg D. Cochlear implants and rehabilitative practices. In: *Handbook of Hearing Aid Amplification*. Sandlin R, ed. Boston: College Hill Press, 1990, pp. 179–188.

[24]Weber BP, Neuburger J, Goldring JE, et al. Clinical results of the CLARION magnetless cochlear implant. *Ann Otol Rhinol Laryngol Suppl* 1999;177:22–26.

[25]Youssefzadeh S, Baumgartner W, Dorffner R, et al. MR compatibility of Med EL cochlear implants: clinical testing at 1.0 T. *J Comput Assist Tomogr* 1998;22:346–350.

[26]Heller JW, Brackmann DE, Tucci DL, et al. Evaluation of MRI compatibility of the modified nucleus multichannel auditory brainstem and cochlear implants. *Am J Otol* 1996; 17:724–729.

[27]Baumgartner WD, Youssefzadeh S, Hamzavi J, et al. Clinical application of magnetic resonance imaging in 30 cochlear implant patients. *Otol Neurotol* 2001;22:818–822.

[28]Schmerber S, Reyt E, Lavieille JP. Is magnetic resonance imaging still a contraindication in cochlear-implanted patients? *Eur Arch Otorhinolaryngol* 2003;260:293–294.

[29]Teissl C, Kremser C, Hochmair ES, et al. Cochlear implants: in vitro investigation of electromagnetic interference at MR imaging—compatibility and safety aspects. *Radiology* 1998;208:700–708.

[30]Nadol JB. Patterns of neural degeneration in the human cochlea and auditory nerve: implications for cochlear implantation. *Otolaryngol Head Neck Surg* 1997;117:220–228.

[31]Linthicum FH, Fayad J, Otto SR, et al. Cochlear implant histopathology. *Am J Otol* 1991;12:245–311.

[32]Woolley AL, Oser AB, Lusk RP, et al. Pre-operative temporal bone computed tomography scan and its use in evaluating the pediatric cochlear implant candidate. *Laryngoscope* 1997;108:1100–1106.

[33]Cohen NL, Hoffman RA, Stroschein M. Medical or surgical complications related to the Nucleus multichannel cochlear implant. *Ann Otol Rhinol Laryngol Suppl* 1988;135:8–13.

[34]Cohen NL, Hoffman RA. Complications of cochlear implant surgery in adults and children. *Ann Otol Rhinol Laryngol* 1991;100:708–711.

[35]Luetje CM, Jackson K. Cochlear implants in children: what constitutes a complication? *Otolaryngol Head Neck Surg* 1997;117:243–247.

[36]Kempf HG, Johann K, Weber BP, et al. Complications of cochlear implant surgery in children. *Am J Otol* 1997;18:S62–S63.

[37]Gysin C, Papsin BC, Daya H, Nedzelski J. Surgical outcome after paediatric cochlear implantation: diminution of complications with the evolution of new surgical techniques. *J Otolaryngol* 2000 Oct;29(5):285–289.

[38]Bielamowiez SA, Coker NJ, Jenkins HA, et al. Surgical dimensions of the facial recess in adults and children. *Arch Otolaryngol Head Neck Surg* 1988;114:534–537.

[39]Eby TL. Development of the facial recess: implications for cochlear implantation. *Laryngoscope* 1996;106(Suppl 80):1–7.

[40]Eby TL, Nadol JB. Postnatal growth of the human temporal bone: implications for cochlear implants in children. *Ann Otol Rhinol Laryngol* 1986;95:356–382.

[41]Dahm MC, Shepherd RK, Clark GM. The postnatal growth of the temporal bone and its implications for cochlear implantation in children. *Acta Otolaryngol Suppl* 1993;505:1–39.

[42]Xu J, Shepherd RK, Xu SA, Seldon HL, Clark GM. Pediatric cochlear implantation: radiologic observations of skull growth. *Arch Otolaryngol Head Neck Surg* 1993;119:525–534.

[43]Burton MJ, Shepherd RK, Xu SA, et al. Cochlear implantation in young children: histological studies on head growth, leadwire, design, electrode fixation in the monkey model. *Laryngology* 1994;104:167–175.

[44]Roland JT Jr, Fishman AJ, Waltzman SB, et al. Stability of the cochlear implant array in children. *Laryngoscope* 1998;108:1119–1123.

[45]Wang RC, Parisier SC, Weiss MH, et al. Cochlear implant flap complications. *Ann Otol Rhinol Laryngol* 1990;99:791–795.

[46]O'Donoghue GM, Nikolopoulos TP. Minimal access surgery for pediatric cochlear implantation. *Otol Neurotol* 2002;23:891–894.

[47]Green JD, Marion MS, Hinojosa R. Labyrinthitis ossificans: histopathologic consideration for cochlear implantation. *Otolaryngol Head Neck Surg* 1991;104:320–326.

[48]Telian SA, Zimmerman-Phillips S, Kileny PR. Successful revision of failed cochlear implants in severe labyrinthitis ossificans. *Am J Otol* 1996;17:53–60.

[49]Nadol JB. Patterns of neural degeneration in the human cochlea and auditory nerve: implications for cochlear implantation. *Otolaryngol Head Neck Surg* 1997;117:220–228.

[50]Balkany T, Gantz B, Nadol JB. Multichannel cochlear implants in obstructed and obliterated cochleas. *Otolaryngol Head Neck Surg* 1988;98:72–81.

[51]Linthicum FH, Fayad J, Otto SR, et al. Cochlear implant histopathology. *Am J Otol* 1991;12:245–311.

[52]El-Kashlan HK, Ashbaugh C, Zwolan T, et al. Cochlear implantation in prelingually deaf children with ossified cochleae. *Otol Neurotol* 2003;24:596–600.

[53]Steenerson RL, Gary LB. Multichannel cochlear implantation in children with cochlear ossification. *Am J Otol* 1999;20:442–444.

[54]Hodges AV, Balkany TJ, Gomez-Marín O, et al. Speech recognition after implantation of the ossified cochlea. *Am J Otol* 1999;20:453–456.

[55]Dodds A, Tyszkiewicz E, Ramsden R. Cochlear implantation after bacterial meningitis: the dangers of dealy. *Arch Dis Child* 1997;76:139–140.

[56]Balkany T, Gantz BJ, Steenerson RL, et al. Systematic approach to electrode insertion in the ossified cochlea. *Otolaryngol Head Neck Surg* 1996;114:4–11.

[57]Gantz BJ, McCabe BF, Tyler RS. Use of multichannel cochlear implants in obstructed and obliterated cochleas. *Otolaryngol Head Neck Surg* 1988;98:72–81.

[58]McClay JE, Tandy R, Grundfast K, et al. Major and minor temporal bone abnormalities in children with and without congenital sensorineural hearing loss. *Arch Otolaryngol Head Neck Surg* 2002;128:664–671.

[59]Ohlms LA, Edwards MS, Mason EO, et al. Recurrent meningitis and Mondini dysplasia. *Arch Otolaryngol Neck Surg* 1990;116:608–612.

[60]Tucci DL, Telian SA, Zimmerman-Phillips S, et al. Cochlear implantation in patients with cochlear malformations. *Arch Otolaryngol Head Neck Surg* 1995;21:833–838.

[61]Jackler RK, Luxford WM, House WF. Congenital malformations of the inner ear: a classification based on embryogenesis. *Laryngoscope* 1987;97(Suppl 40):15–17.

[62]Shelton C, Luxford WM, Tonokawa LL, et al. The narrow internal auditory canal in children: a contraindication for cochlear implants. *Otolaryngol Head Neck Surg* 1989;100: 227–231.

[63]Casselman JW, Offeciers FE, Govaerts PJ, et al. Aplasia and hypoplasia of the vestibulocochlear nerve: diagnosis with MR imaging. *Radiology* 1997; 202:773–781.

[64]Otte G, Schuknecht HF, Kerr AG. Ganglion cell populations in normal and pathological human cochleae: implications for cochlear implantation. *Laryngoscope* 1978;88:1231–1246.

[65]Johnsson LG, Hawkins JE, Rouse RC, et al. Four variations of the Mondini inner ear malformations as seen in microdissections. *Am J Otol* 1984;5:242–257.

[66]Monsell EM, Jackler RK, Motta G, et al. Congenital malformations of the inner ear. *Laryngoscope* 1987;97(Suppl 40):18–24.

[67]Zheng Y, Schachern PA, Cureoglu S, et al. The shortened cochlea: its classification and histopathologic features. *Int J Pediatr Otorhinolaryngol* 2002;63:29–39.

[68]Molter DW, Pate BR, McElveen JT. Cochlear implantation in the congenitally malformed ear. *Otolaryngol Head Neck Surg* 1993;108:174–177.

[69]Hoffman RA, Downey LL, Waltzman SB, et al. Cochlear implantation in children with cochlear malformations. *Am J Otol* 1997;18:184–187.

[70]Weber BP, Dillo W, Dietrich B, et al. Pediatric cochlear implantation in cochlear malformations. *Am J Otol* 1998;19:747–753.

[71]Woolley AL, Jenison V, Stroaer BS, et al. Cochlear implantation in children with inner ear malformations. *Ann Otol Rhinol Laryngol* 1998;107:492–500.

[72]Eisenman DJ, Ashbaugh C, Zwolan TA, et al. Implantation of the malformed cochlea. *Otol Neurotol* 2001;22:834–841.

[73]Incesulu A, Vural M, Erkan U, et al. Cochlear implantation in children with inner ear malformations: report of two cases. *Int J Pediatr Otorhinolaryngol* 2002;65:171–179.

[74]Buchman CA, Copeland BJ, Yu KK, et al. Cochlear implantation in children with congenital inner ear malformations. *Laryngoscope* 2004;114:309–316.

[75]Govaerts PJ, Casselman J, Daemers K, et al. Cochlear implants in aplasia and hypoplasia of the cochleovestibular nerve. *Otol Neurotol* 2003;24:887–891.

[76]Mylanus EAM, Rotteveel LJC, Leeuw RL. Congenital malformation of the inner ear and pediatric cochlear implantation. *Otol Neurotol* 2004;25:308–317.

[77]Cohen NL. Cochlear implant soft surgery: fact or fantasy? *Otolaryngol Head Neck Surg* 1997;117:214–216.

[78]Clark GM. An evaluation of per-scalar cochlear electrode implantation techniques: a histopathological study in cats. *J Laryngol Otol* 1977;91:185–199.

[79]Shepherd RK, Clark GM, Black RC. Chronic electrical stimulation of the auditory nerve in cats. *Acta Otolaryngol (Stockh) Suppl* 1983;399:19–31.

[80]Kennedy DW. Multichannel intracochlear electrodes: mechanism of insertion trauma. *Laryngoscope* 1987;97:42–49.

[81]Cohen NL, Hoffman RA. Complications of cochlear implant surgery. In: *Complications in Head and Neck Surgery*. Krespi YP, Ossoff RH, eds. Baltimore, Md.: Mosby, 1993.

[82]House JR, Luxford WM. Facial nerve injury in cochlear implantation. *Otolaryngol Head Neck Surg* 1993;109:1078–1082.

[83]Fayad JN, Wanna GB, Micheletto JN, et al. Facial nerve paralysis following cochlear implant surgery. *Laryngoscope* 2003;113:1344–1346.

[84]House WF, Luxford WM, Courtney B. Otitis media in children following cochlear implant. *Ear Hear* 1985;6:24S–26S.

[85]Luntz M, Hodges AV, Balkany T, et al. Otitis media in children with cochlear implants. *Laryngoscope* 1996;106:1403–1405.

[86]Fayad JN, Tabaee A, Micheletto JN, et al. Cochlear implantation in children with otitis media. *Laryngoscope* 2003;113:1224–1227.

[87]Kempf HG, Stöver T, Lenarz T. Mastoiditis and acute otitis media in children with cochlear implants: recommendations for medical management. *Ann Otol Rhinol Laryngol Suppl* 2000;185:25–27.

[88]Papsin BC, Bailey CM, Albert DM, et al. Otitis media with effusion in paediatric cochlear implantees: the role of peri-implant grommet insertion. *Int J Pediatr Otorhinolaryngol* 1996; 38:13–19.

[89]Nadol JB, Eddington DK. Histologic evaluation of the tissue seal and biologic response around cochlear implant electrodes in the human. *Otol Neurotol* 2004;25:257–262.

[90]Antonelli PJ, Lee JC, Burne RA. Bacterial biofilms may contribute to persistent cochlear implant infection. *Otol Neurotol* 2004 Nov;25(6):953–957.

[91]Reefhuis J, Honein MA, Whitney CG, et al. Risk of bacterial meningitis in children with cochlear implants. *N Engl J Med* 2003;349:435–445.

[92]Callanan V, Poje C. Cochlear implantations and meningitis. *Int J Pediatr Otorhinolaryngol* 2004;68:545–550.

[93]Page EL, Eby TL. Meningitis after cochlear implantation in Mondini malformation. *Otolaryngol Head Neck Surg* 1997;116:104–106.

[94]Suzuki C, Sando I, Fagan JJ, et al. Histopathological features of a cochlear implant and otogenic meningitis in Mondini dysplasia. *Arch Otolaryngol Head Neck Surg* 1998;124: 462–466.

[95]O'Donoghue GM, Balkany T, Cohen N, et al. Meningitis and cochlear implantation. *Otol Neurotol* 2002;23:823–824.

[96]Cohen NL, Roland JT, Marrinan M. Meningitis in cochlear implant recipients: the North American experience. *Otol Neurotol* 2004;25:275–281.

[97]Pneumococcal vaccination for cochlear implant candidates and recipients: updated recommendations of the advisory committee on immunization practices. *MMWR Morb Mortal Wkly Rep* 2003;52(31):739–740.

[98]Ito J, Sakakihara J. Tinnitus suppression by electrical stimulation of the cochlear wall and by cochlear implantation. *Laryngoscope* 1994;104:752–754.

[99]Souliere CRJ, Kileny PR, Zwolan TA, et al. Tinnitus suppression following cochlear implantation: a multifactorial investigation. *Arch Otolaryngol Head Neck Surg* 1992;118: 1291–1297.

[100]Tyler RS. Tinnitus in the profoundly hearing-impaired and the effects of cochlear implants. Ann Otol Rhinol Laryngol Suppl 1995;165:25.

[101]Ruckenstein MJ, Hedgepeth C, Rafter KO, et al. Tinnitus suppression in patients with cochlear implants. *Otol Neurotol* 2001;22:200–204.

[102]Miyamoto RT, Bichey BG. Cochlear implantation for tinnitus suppression. *Otolaryngol Clin North Am* 2003;36:345–352.

[103]Aschendorff A, Pabst G, Klenzner T, et al. Tinnitus in cochlear implant users: the Freiburg experience. *Int Tinnitus J* 1998;4:162–164.

[104]Vibert D, Hausler R, Kompis M, et al. Vestibular function in patients with cochlear implantation. *Acta Otolaryngol Suppl* 2001;545:29–34.

[105]Dobie R, Jenkins H, Cohen N. Surgical results. *Ann Otol Rhinol Laryngol* 1995; 104(Suppl 165):6–8.

[106]Kubo T, Yamamoto K, Iwaki T, et al. Different forms of dizziness occurring after cochlear implant. *Eur Arch Otorhinolaryngol* 2001;258:9–12.

[107]Ito J. Influence of the multichannel cochlear implant on vestibular function. *Otolaryngol Head Neck Surg* 1998;118:900–902.

[108]Fina M, Skinner M, Goebel JA, et al. Vestibular dysfunction after cochlear implantation. *Otol Neurotol* 2003;24:234–242.

[109]Steenerson RL, Cronin GW, Gary LB. Vertigo after cochlear implantation. *Otol Neurotol* 2001;22:842–843.

[110]Hoffman RA, Cohen NL. Complications of cochlear implant surgery. *Ann Otol Rhinol Laryngol* 1995;166:420–422.

[111]Gibson WPR, Harrison HC. Further experience with a straight, vertical incision for placement of cochlear implants. *J Laryngol Otol* 1997;111:924–927.

[112]Harris JP, Cueva RA. Flap design for cochlear implantation: avoidance of a potential complication. *Laryngoscope* 1987;97:755–757.

[113]Gibson WPR, Harrison HC, Prowse C. A new incision for placement of cochlear implants. *J Laryngol Otol* 1995;109:821–825.

[114]Cohen NL, Hoffman RA. Complications of cochlear implant surgery. In: *Complications in Head and Neck Surgery*. Baltimore, Md.: Mosby, 1993:723.

[115]Wang RC, Parisier SC, Weiss MH, et al. Cochlear implant flap complications. *Ann Otol Rhinol Laryngol* 1990;99:791–795.

[116]Haberkamp TJ, Schwaber MK. Management of flap necrosis in cochlear implantation. *Ann Otol Rhinol Laryngol* 1992;101:38–41.

[117]Kennedy DW. Multichannel intracochlear electrodes: mechanism of insertion trauma. *Laryngoscope* 1987;97:42–49.

[118]Fayad J, Linthicum FH, Otto SR, et al. Cochlear implants: histopathologic findings related to performance in 16 human temporal bones. *Ann Otol Rhinol Laryngol* 1991;100: 807–811.

[119]Zappia JJ, Niparko JK, Oviatt DL, et al. Evaluation of the temporal bones of a multichannel cochlear implant patient. *Ann Otol Rhinol Laryngol* 1991;100:914–921.

[120]Nadol JB, Ketten DR, Burgess BJ. Otopathology in case of multichannel cochlear implantation. *Laryngoscope* 1994;104:299–303.

[121]Zappia JJ, Niparko JK, Oviatt DL, et al. Evaluation of the temporal bones of a multichannel cochlear implant patient. *Ann Otol Rhinol Laryngol* 1991;100:914–921.

[122]Shepherd RK, Clark GM, Black RC. Chronic electrical stimulation of the auditory nerve in cats. *Acta Otolaryngol (Stockh) Suppl* 1983;399:19–31.

[123]Clark FM, Shepherd RK, Franz BK-H. The histopathology of the human temporal bone and auditory central nervous system following cochlear implantation in a patient. *Acta Otolaryngol (Stockh) Suppl* 1988;448:6–65.

[124]Linthicum, FH, Fayad J, Otto SR, et al. Cochlear implant histopathology. *Am J Otol* 1991;12:245–311.

[125]Nadol JB Jr, Shiao JY, Burgess BJ, et al. Histopathology of cochlear implants in humans. *Ann Otol Rhinol Laryngol* 2001;110:883–891.

[126]Leake PA, Hradek GT, Snyder RL. Chronic electrical stimulation by a cochlear implant promotes survival of spiral ganglion neurons after neonatal deafness. *J Comp Neurol* 1999; 412:543–562.

[127]Li L, Parkins CW, Webster DB. Does electrical stimulation of deaf cochleae prevent spiral ganglion degeneration? *Hear Res* 1999;133:27–39.

[128]*Cochlear Americas Technology Update*, Vol.1, Ed. 2, October 2004.

[129]Weise JB, Muller-Deile J, Brademann G, Meyer JE, Ambrosch P, Maune S. Impact to the head increases cochlear implant reimplantation rate in children. *Auris Nasus Larynx* 2005 May 26; [Epub ahead of print].

[130]Alexiades G, Roland JT, Fishman AJ, et al. Cochlear reimplantation: surgical techniques and functional results. *Laryngoscope* 2001;111:1608–1613.

[131]Luetje CM, Jackson K. Cochlear implants in children: what constitutes a complication. *Otolaryngol Head Neck Surg* 1997;117:243–247.

[132]Parisier SC, Chute PM, Popp AL. Cochlear implant mechanical failures. *Am J Otol* 1996;17:730–734.

[133]Miyamoto RT, Svirsky MA, Myres WA, et al. Cochlear implant reimplantation. *Am J Otol* 1997;18:S60–S61.

[134]Balkany TJ, Hodges AV, Gómez-Marín O, et al. Cochlear reimplantation. *Laryngoscope* 1999;109:351–355.

[135]Alexiades G, Roland JT, Fishman AJ, et al. Cochelar reimplantation: surgical techniques and functional results. *Laryngoscope* 2001;111:1608–1613.

[136]Parisier SC, Chute PM, Popp AL, et al. Outcome analysis of cochlear implant reimplantation in children. *Laryngoscope* 2001;111:26–32.

[137]Haensel J, Engelke JC, Dujardin H, et al. Cochlear reimplantation—experiences and results. *Laryngorhinootologie* 2004;83:83–87.

[138]Brackett D, Zara CV. Communication outcomes related to early implantation. *Am J Otol* 1998;19:453–460.

[139]Nikolopoulos TP, O'Donoghue GM, Archbold S. Age at implantation: its importance in pediatric cochlear implantation. *Laryngoscope* 1999;109:595–599.

[140]Hammes DM, Novak MA, Rotz LA, et al. Early identification and cochlear implantation: critical factors for spoken language development. *Ann Otol Rhinol Laryngol Suppl* 2002;189:74–78.

[141]Robbins AM, Koch DB, Osberger MJ. Effect of age at cochlear implantation on auditory skill development in infants and toddlers. *Arch Otolaryngol Head Neck Surg* 2004;130:570–574.

[142]Geers AE. Speech, language, and reading skills after early cochlear implantation. *Arch Otolaryngol Head Neck Surg* 2004;130:634–638.

[143]Dowell RC, Dettman SJ, Hill K, et al. Speech perception outcomes in older children who use multichannel cochlear implants: older is not always poorer. *Ann Otol Rhinol Laryngol Suppl* 2002;189:97–101.

[144]Staller SJ, Beiter AL, Brimacombe JA, et al. Pediatric performance with the Nucleus 22-channel cochlear implant system. *Am J Otol* 1991;12 Suppl:126–136.

[145]Tobey EA, Rekard D, Buckley K, et al. Mode of communication and classroom placement impact on speech intelligibility. *Arch Otolaryngol Head Neck Surg* 2004;130:639–643.

[146]Dillon C, Pisoni DB, Cleary M, et al. Nonword imitation by children with cochlear implants. *Arch Otolaryngol Head Neck Surg* 2004;130:587–591.

[147]Nikolopoulos TP, Gibbin KP, Dyar D. Predicting speech perception outcomes following cochlear implantation using Nottingham children's implant profile (NChIP). *Int J Pediatr Otorhinolaryngol* 2004;68:137–141.

[148]Spahn C, Richter B, Zschocke I, et al. The need for psychosocial support in parents with cochlear implanted children. *Int J Pediatr Otorhinolaryngol* 2001;57:45–53.

[149]O'Neill C, O'Donoghue GM, Archbold SM, et al. A cost-utility analysis of pediatric cochlear implantation. *Laryngoscope* 2000;110:156–160.

[150]Cheng AK, Rubin HR, Powe NR, et al. Cost-utility analysis of the cochlear implant in children. *JAMA* 2000;284:850–856.

[151]Institute of Medicine, Committee on Postmarket Surveillance of Pediatric Medical Devices. *Safe Medical Devices for Children.* Field M, and Tilson H, eds. Washington, DC: The National Academies Press, 2005.

[152] Tambyraja EM, Gutman MA, Megerian CA Cochlear implant complications: Utility of federal database in systematic analysis. *Archives of Otolaryngology-Head & Neck Surgery*, 2005, Mar;131(3):245-250.

G

Glossary

Active surveillance. For adverse event reporting, programs that include direct involvement by the sponsor (e.g., U.S. Food and Drug Administration [FDA]) in collecting information, for example, through routine or special surveys. (See also Passive surveillance.)

Adolescent. As defined by FDA in connection with medical devices, an individual between the ages of 12 and 20 ("up to 21" years).

Adverse event. An instance of harm during patient care or research that is not the result of the individual's disease or medical condition. Adverse events are sometimes defined to include events that have the potential to cause harm, such as *close calls* or *near misses* that could have resulted in harm but did not.

Approval. Authorization to market a medical device that requires submission of a premarket approval application (PMA) and FDA review of safety and effectiveness.

Benefit. A positive or valued outcome of an action or event.

Child. As defined by FDA in connection with medical devices, an individual between the ages of 2 and 11 ("up to 12" years).

Class I medical devices. Low-risk devices that need not be reviewed by FDA before marketing As specified in statute, these are (1) devices for which certain "general" controls, for example, standards for good manufacturing practices, are considered to provide reasonable assurance of the safety and effectiveness of the device or (2) devices that are not intended or represented ("purported") to support or sustain life or play an important role in preventing impairment or that are not

expected to pose an unreasonable risk of illness or injury. (21 USC 360c(a)(1)(A))

Class II medical devices. Devices that present more risk than Class I devices (see above). For these devices, general controls are not by themselves sufficient to provide reasonable assurance of safety and effectiveness, but sufficient information is available to develop "special controls" (for example, guidelines) for that purpose (21 USC 360(c)(a)(1)). For a Class II device to be legally marketed, the manufacturer must usually submit a notification of intent to market and receive FDA clearance under 510(k) provisions (referring to the applicable section of the Medical Device Amendments of 1976. (21 USC 360(k))

Class III medical devices. Devices that are intended to support or sustain life or play an important role in preventing impairment or that are considered to pose an unreasonable risk of illness or injury. For devices in this class, FDA has determined that general controls are inadequate to reasonably assure safety and effectiveness and that available information is insufficient to develop adequate special controls. (21 USC 360(c)(a)(1)) Class III devices usually require FDA approval.

Clearance. A process for FDA to authorize a device for marketing based on a review of evidence of safety and equivalence to certain previously marketed devices; clinical evidence of safety and effectiveness is not usually required.

Clinical trial. A prospective study involving human subjects that is designed to evaluate a health care intervention (e.g., device therapy, diagnostic test).

Close call (see Near miss).

Combination product. A product that (1) is comprised of two or more regulated components, i.e., drug/device, biologic/device, drug/biologic, or drug/device/biologic, that are physically, chemically, or otherwise combined or mixed and produced as a single entity; (2) is comprised of two or more separate products packaged together in a single package or as a unit and comprised of drug and device products, device and biological products, or biological and drug products; or (3) is packaged separately that according to its investigational plan or proposed labeling is intended for use only with an approved individually specified drug, device, or biological product where both are required to achieve the intended use, indication, or effect and where upon approval of the proposed product the labeling of the approved product would need to be changed, e.g., to reflect a change in intended use, dosage form, strength, route of administration, or significant change in dose. (21 CFR 3.2(e))

Compassionate use. A mechanism for securing FDA permission for the use with an individual patient of a medical device that has not been approved or cleared for marketing. (See also Emergency use.)

Condition-of-approval study. A study to be conducted after approval of a device to address issues of safety and effectiveness (e.g., long-term effects, effects in populations not yet studied) not sufficiently evaluated by studies submitted in support of a premarket approval application. The manufacturer agrees to perform these studies as a condition of approval.

Confidential commercial information. Valuable data or information that is used in one's business and is of a type customarily held in strict confidence or regarded as privileged and not disclosed to any member of the public by the person to whom it belongs. (21 CFR. 20.61)

Correction. A type of recall that involves an on-site repair, adjustment, labeling change, destruction, or inspection of a product.

Corrective action. Action to eliminate the cause(s) of an existing defect or similar product or quality problem in order to prevent recurrence.

Design controls. Procedures to control the design of the device in order to ensure that specified design requirements are met. (21 CFR 820.30)

Device failure. The failure of a device to perform or function as intended, including any deviations from the device's performance specifications or intended use. (21 CFR 822.3(c))

Device malfunction. The failure of a device to meet its performance specifications or otherwise perform as intended. (21 CFR 803.3(n))

Device tracking. A process that allows manufacturers to provide certain critical information about the location of certain Class II or III devices so that they can promptly remove a device from the market when requried by the FDA.

Direct benefit. A tangible positive outcome of an event or action.

Distributor. Any person who furthers the distribution of a device from the original place of manufacture to the person who makes delivery or sale to the ultimate user. (21 CFR 821.3(h))

Effectiveness. The achievement of desired results in actual clinical practice.

Efficacy. The achievement of desired results in controlled clinical studies.

Explant. An implanted device that has been removed from a patient.

General controls. Requirements (e.g., registering all manufacturing locations, following quality system regulations) that all classes of medical devices must meet to be lawfully marketed.

Harm. A hurtful or adverse outcome of an action or event, whether temporary or permanent.

Hazard. A potential source of harm.

Human factors. [H]ow people use technology . . . the interaction of human abilities, expectations, and limitations, with work environments and system design (FDA, 2003s).

Humanitarian Device Exemption (HDE) application. An application that is similar to a premarket approval (PMA) application but exempt from

the effectiveness requirements of a PMA. An approved HDE authorizes marketing of a Humanitarian Use Device.

Humanitarian Use Device. A device that is intended to benefit patients suffering from a disease or condition that affects fewer than 4,000 individuals in the United States per year.

Implant. As defined in regulations for investigational devices: a device that is placed into a surgically or naturally formed cavity of the human body if it is intended to remain there for a period of 30 days or more. To protect public health, FDA may also determine that devices placed in subjects for shorter periods are also "implants." (21 CFR 812.3(d)) As defined in medical device tracking regulations: a device that is intended to be placed into a surgically or naturally formed cavity of the human body for more than 1 year to continuously assist, restore, or replace the function of an organ system or structure of the human body throughout the useful life of the device. (21 CFR 821.3(f))

Importer. One who imports a device into the United States and who furthers the marketing of a device from the original place of manufacture to the person who makes final delivery or sale to the ultimate user. Does not include those who repackage or otherwise change the container, wrapper, or labeling of the device or device package.

Infant. As used by FDA in relation to medical devices, individual below 2 years of age.

Institutional Review Board (IRB). A group of qualified individuals charged under federal regulation with protecting the rights and welfare of people involved in research in accord with federal regulations. IRBs review and approve plans for research involving humans.

Investigational device. A device that is the object of a clinical investigation or research involving one or more subjects to determine safety or effectiveness of the device. (21 CFR 812.3(g) & (h))

Label. A display of written, printed, or graphic matter upon the immediate container of a drug or other product. (FDCA 201(k))

Malfunction. The failure of a device to meet its performance specifications or to perform as intended. (21 CFR 803.3(n))

Manufacturer. Any person, including any importer (i.e., an initial distributor of an imported device), repacker, relabeler, or specifications developer who manufactures, prepares, propagates, compounds, assembles, or processes a device. (21 CFR 821.3(c))

Market withdrawal. A firm's removal or correction of a distributed product which involves a minor violation that would not be subject to legal action by the FDA or which involves no violation, e.g., normal stock rotation practices, routine equipment adjustments and repairs, etc. (FDA, 2002i).

Medical device. An instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including a component, part, or accessory, which is
- recognized in the official National Formulary, or the United States Pharmacopoeia, or any supplement of them;
- intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals; or
- intended to affect the structure or any function of the body of man or other animals; and
- which does not achieve any of its primary intended purposes through chemical action within or on the body of man of other animals and which is not dependent upon being metabolized for the achievement of its primary intended purposes. (21 USC 321(h))

Misbranded. A device is considered misbranded if it fails to meet any one of several requirements, for example, if its labeling is false or misleading or if it was made in an establishment that was not registered in accord with regulations. (21 USC 352)

Near miss. An event that could have resulted in harm but did not. Sometimes described as a "close call."

Nonsignificant risk device. A device that does not pose a significant risk to the human research subjects. Studies involving such devices require IRB approval and informed consent but do not require an Investigational Device Exemption (IDE) from FDA. (See also Significant risk device.)

Off-label use. (See Unlabeled use.)

Passive surveillance. For adverse event reporting, a program that waits for reports from individuals or organizations without active efforts to collect information. (See Active surveillance.)

Pediatric population. May refer to all children or a subgroup of children who share the same characteristics.

Permanently implantable device. An implantable device is a device that is intended to be placed into a surgically or naturally formed cavity of the human body for more than 1 year to continuously assist, restore, or replace the function of an organ system or structure of the human body throughout the useful life of the device.

Postamendment device. A medical device available to consumers after the enactment of the Medical Device Amendments of 1976.

Postmarket. Processes including evaluations, activities, and decisions that occur after regulatory approval, clearance, or registration of a medical product for marketing.

Postmarket study commitments. Refers collectively to condition-of-approval studies and Section 522 Postmarket Surveillance studies.

Postmarket surveillance of medical devices. Programs that seek to protect

public health by systematically collecting, analyzing, and communicating information about events involving or potentially involving legally marketed medical devices.

Postmarket Surveillance (Section 522) study. Required postmarket activity that may be ordered after the approval or clearance of certain Class II or Class III devices.

Preamendment device. A medical device available to consumers before enactment of the Medical Device Amendments of 1976. (See Predicate device.)

Predicate device. A device that a) was legally marketed in the U.S. prior to May 28, 1976, or b) has been reclassified from Class III to Class II or I, OR c) was found to be substantially equivalent through the premarket notification (510(k)) process.

Premarket. Processes including evaluations, decisions, and other activities that occur prior to the marketing of a medical product.

Premarket notification (510(k) process). Process for securing FDA clearance to market devices that are substantially equivalent to devices marketed prior to May 28, 1976. 510(k) refers to the relevant section of the Federal Food, Drug, and Cosmetic Act.

Public health notification. An FDA announcement used to quickly disseminate device-related safety information beneficial to healthcare providers. Recently the FDA decided to comprehensively apply the term to what had been distinguished as Safety Alerts, Public Health Notifications, and Public Health Advisories.

Quality systems regulation. General control requirements that cover methods, facilities and controls related to medical device design (prior to actual production), manufacture, packing, storage, and installation. These regulations include Good Manufacturing Practices and seek to prevent safety problems related to design deficiencies.

Rare condition. A condition that affects or is manifested in (causes symptoms in) fewer than 4,000 individuals in the United States per year.

Recall. A firm's voluntary or directed removal or correction of a marketed product that the FDA considers to be in violation of the laws it administers and against which the agency would initiate legal action, e.g., seizure. Recall does not include a market withdrawal or a stock recovery. (21 CFR 7) *Class I recalls* involve dangerous or defective products that have a reasonable probability of causing serious health problems or death. *Class II recalls* involve products that might be expected to cause a temporary health problem or that pose only a slight threat of a serious nature. *Class III recalls* involve products that are unlikely to cause any adverse health reaction, but that violate FDA labeling or manufacturing regulations.

Registry. A system for collecting information about a class of individuals or patients who have in common a disease, injury, condition, medical pro-

cedure or product, or similar characteristic. The term registry is sometimes used narrowly to refer to the database itself and sometimes more broadly to refer to analyses and studies based on registry information.

Risk. A potential harm or the potential of an action or event to cause harm.

Risk management. A systematic application of policies, procedures, and practices to the analysis, evaluation, and control of risks. It is a key component of quality management systems, and a central requirement of the implementation of Design Controls in the Quality Systems Regulation (FDA, 2000b).

Safe. A relative term, defined as: "there is reasonable assurance that a device is safe when it can be determined, based upon valid scientific evidence, that the probable benefits to health from use of the device for its intended uses and conditions of use, when accompanied by adequate directions and warnings against unsafe use, outweigh any probable risks." (21 CFR 860.7(d)(1))

Safety alert (see Public health notification).

Safety signal. An apparent excess of reported adverse events associated with a product. Sometimes a single, well-documented report may be sufficient to signal a safety problem.

Serious adverse health consequence. Any significant adverse experience related to a device, including events which are life threatening or which involve permanent or long-term injury or illness. (21 CFR 821.3(e))

Serious injury. An injury or illness that (1) is life threatening; (2) results in permanent impairment of a body function or permanent damage to body structure; or (3) requires medical or surgical intervention to preclude permanent impairment or damage.

Significant risk device. A device that cannot undergo tests in humans without IRB approval and FDA approval of an application for an Investigational Device Exemption. Such a device is one that: (1) is intended as an implant and presents a potential for serious risk to the health, safety, or welfare of a subject; (2) is purported or represented to be for a use in supporting or sustaining human life and presents a potential for serious risk to the health, safety, or welfare of a subject; (3) is for a use of substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise preventing impairment of human health and presents a potential for serious risk to the health, safety, or welfare of a subject; or (4) otherwise presents a potential for serious risk to the health, safety, or welfare of a subject. (21 CFR 812.3(m))

Special controls. Requirements for Class II medical devices that are intended to ensure safety and effectiveness. Unlike general controls, special controls may vary for different types of devices. Special controls

include performance standards, guidelines, patient registries, and post-market surveillance. (FDCA section 513(a)(1)(B))

Substantially equivalent. When a device (a) has same intended use and has same technological characteristics as a predicate device, OR (b) has the same intended use but different technological characteristics *if* these differences do not raise different questions of safety and effectiveness *and if* information is provided to show that the device is as safe and effective a legally marketed device.

Surveillance. The ongoing, systematic collection, analysis, interpretation, and dissemination of data about a health-related event for use in public health action to reduce morbidity and mortality and to improve health (CDC, 2001).

Trade Secret. Information that may consist of any commercially valuable plan, formula, process, or device that is used for the making, preparing, compounding, or processing of trade commodities and that can be said to be the end product of either innovation or substantial effort. There must be a direct relationship between the trade secret and the productive process.

Unlabeled use. Use of a drug or medical device for a purpose, patient group, or other use that is not specifically approved by the FDA for use as indicated on the product's label. Such use by physicians is considered part of the practice of medicine, which FDA—by statute—does not regulate. Sometimes described as "off-label" use.

User facility. A hospital, an ambulatory surgical facility, a nursing home, an outpatient diagnostic facility, or an outpatient treatment facility that is not a physician's office. An outpatient treatment facility includes home health care groups, ambulance providers, and rescue services. (21 CFR 803.3(f) & (v))

Withdrawal of FDA approval. An order withdrawing approval of a PMA if, from any information available to the Agency, FDA determines that certain requirements were not fulfilled. (21 CFR 814.46(a))

ACRONYMS AND ABBREVIATIONS

510(k)	premarket notification
AAP	American Academy of Pediatrics
ACC	American College of Cardiology
ACHRE	Advisory Committee on Human Radiation Experiments
AHRQ	Agency for Health Research and Quality
AMA	American Medical Association
AMC	academic medical center
CBER	Center for Biologics Evaluation and Research
CDC	Centers for Disease Control and Prevention

CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CERT	Centers for Education and Research on Therapeutics
CHCA	Child Health Corporation of America
CMS	Centers for Medicare and Medicaid Services
CONSORT	Consolidated Standard of Reporting Trials
CRO	contract research organization
CT	computer-assisted tomography
DHHS	U.S. Department of Health and Human Services
DSaRM	Drug Safety and Risk Management Advisory Committee
ECLS	Extracorporeal Life Support
ECMO	Extracorporeal Membrane Oxygenation
ECRI	formerly, the Emergency Care Research Institute
EU	European Union
FDA	U.S. Food and Drug Administration
GAO	Government Accountability Office (formerly General Accounting Office)
GHTF	Global Harmonization Task Force
GMDN	Global Medical Device Nomenclature
GMP	Good Manufacturing Practices
HDE	Humanitarian Device Exemption
HIPAA	Health Insurance Portability and Accountability Act of 1996
HUD	Humanitarian Use Device
ICD	International Classification of Diseases
ICH	International Conference on Harmonisation
IDE	Investigational Device Exemption
IOM	Institute of Medicine
IRB	Institutional Review Board
ISO	International Organization for Standardization
ISPE	International Society for Pharmacoepidemiology
JCAHO	Joint Commission on the Accreditation of Healthcare Organizations
LVAD	left ventricular assist device

M-DEN	Medical Device Engineering Network
MDR	Medical Device Reporting
MedSun	Medical Product Surveillance Network
MRI	magnetic resonance imaging
NACHRI	National Association of Children's Hospitals and Related Institutions
NAS	National Academy of Sciences
NEISS	National Electronic Injury Surveillance System
NHLBI	National Heart Lung and Blood Institute
NICHD	National Institute for Child Health and Human Development
NIH	National Institutes of Health
NRC	National Research Council
NYPORTS	New York Patients Occurrence and Tracking System
OIG	Office of Inspector General
PDP	product development protocol
PHTS	Pediatric Heart Transplant Study
PMA	premarket approval application
QuIC	Quality Interagency Coordination Task Force
SEC	Securities and Exchange Commission
STAMP	Systematic Technical Assessment of Medical Products
STROBE	Strengthening the Reporting of Observational studies in Epidemiology
UMDNS	Universal Medical Device Nomenclature System
VAERS	Vaccine Adverse Event Reporting System

PUBLIC LAWS

P.L. 59–384	Pure Food and Drugs Act of 1906
P.L. 75–717	Federal Food, Drug, and Cosmetic Act of 1938
P.L. 87–78	Drug Amendments of 1962
P.L. 94–295	Medical Device Amendments of 1976
P.L. 99–660	National Childhood Vaccine Injury Act of 1986
P.L. 101–629	Safe Medical Devices Act of 1990

P.L. 102–300	Medical Device Amendments of 1992
P.L. 104–191	Health Insurance Portability and Accountability Act of 1996
P.L. 105–115	Food and Drug Administration Modernization
P.L. 106–310	Children's Health Act of 2000
P.L. 107–109	Best Pharmaceuticals for Children Act of 2002
P.L. 107–188	Public Health Security and Bioterrorism Preparedness and Response Act of 2002
P.L. 107–250	Medical Device User Fee and Modernization Act of 2002
P.L. 108–155	Pediatric Research Equity Act of 2003
P.L. 108–214	Medical Devices Technical Corrections Act of 2004

H

Committee Biographical Statements

Hugh Tilson, M.D., Dr.P.H. *(Chair),* is an epidemiologist and outcomes researcher whose career in preventive medicine and public health extends over three decades. He is currently Senior Adviser to the Dean of the University of North Carolina School of Public Health and Clinical Professor of Public Health Leadership and Adjunct Professor of Epidemiology and Health Policy at the University. Dr. Tilson chairs the National Steering Committee for the Centers for Education and Research on Therapeutics (CERTs) program for the Agency for Healthcare Research and Quality. From 1981 to 1996, he was an executive with Burroughs Wellcome and the Wellcome Foundation, where he was responsible for introducing epidemiological methods and principles. He was Founding Co-President of the International Society for Pharmacoepidemiology.

James M. Anderson, Ph.D., M.D., is Professor of Pathology, Macromolecular Science, and Biomedical Engineering in the Institute of Pathology, Case Western Reserve University, Cleveland, Ohio. He is a member of the Institute of Medicine. For the past 13 years, Dr. Anderson has been involved in the International Organization for Standardization (ISO) Task Force to Develop Standards for Medical Device Safety. He is the Chairman for Part 1 of the ISO 10,993 Standard that defines criteria for the biological response evaluation of medical devices, prostheses, and biomaterials. Dr. Anderson's research interests range from his activity as a pathologist in clinical implant retrieval and evaluation to fundamental, mechanistic studies focused on de-

veloping a better understanding of tissue, cell, and blood interactions with biomaterials.

Erle H. Austin, III, M.D., is Professor of Surgery, Division of Thoracic and Cardiovascular Surgery, Department of Surgery, University of Louisville Medical School. He is Chief of cardiovascular surgery at Kosair Children's Hospital and also practices at other Louisville hospitals. He is a member of the Congenital Heart Surgeons' Society (CHSS) and of the Scientific and Government Relations Committee of American Association of Thoracic Surgeons. Dr. Austin's research and policy interests include evaluation of implanted medical devices to treat congenital heart problems and the development of criteria for evaluating the safety and effectiveness of medical devices for pediatric populations.

Mark E. Bruley, is a biomedical engineer and Vice President for Accident and Forensic Investigation at ECRI, an independent nonprofit health services research agency in Plymouth Meeting, Pennsylvania. Since 1982 he has been responsible for ECRI's health technology accident and forensic investigation programs that provide investigative and educational services worldwide. He recently developed the education and training materials for recognition, investigation, and root cause analysis of medical device adverse events in health care facilities for FDA's new MedSun medical device problem reporting program. He publishes, lectures, and consults on medical device accident investigation, medical error and patient safety, problem reporting programs and regulations, and health care technology acquisition.

Paul Citron, M.S.E.E., retired as Vice President for Technology Policy and Academic Relations at Medtronic, Inc., Minneapolis, Minnesota, after 32 years. His entire career at the company related to research and development. He is currently visiting professor at the University of California, San Diego. Mr. Citron was elected to the National Academy of Engineering (NAE) in 2003 for "innovations in technologies for monitoring cardiac rhythm and for patient-initiated cardiac pacing, and for outstanding contributions to industry–academia interactions." He is currently a member of the NAE Division Committee on Engineering and Physical Sciences and the Bioengineering Peer Committee. He is a member of the Roundtable on Biomedical Engineering Materials and Applications. Mr. Citron was a founding member of the American Institute for Medical and Biological Engineering.

William H. DuMouchel, Ph.D., is Vice-President, Research, and Chief Statistical Scientist at Lincoln Technologies, Inc., Wellesley Hills, Massa-

chusetts. He previously was Senior Scientist at AT&T Labs and Research and Professor of Biostatistics and Medical Informatics at Columbia University. He has developed Bayesian methods for disproportionality analysis of databases of spontaneous reports of adverse drug reactions that are now used within FDA and industry. His research has also focused on Bayesian models for data mining and meta-analysis and on computer advisory systems for data analysis. Dr. DuMouchel is an elected fellow of the American Statistical Association and of the Institute of Mathematical Statistics. He served previously on the National Research Council Committee on Applied and Theoretical Statistics.

Ellen J. Flannery, J.D., is a partner at Covington & Burling, Washington, DC. She advises clients regarding the regulation of medical devices, pharmaceuticals, and biological products, as well as product liability law. She has chaired the American Bar Association Section of Science and Technology and the ABA Coordinating Group on Bioethics and the Law. Ms. Flannery has been counsel in cases involving the scope of FDA's legal authority and product liability defense and has taught Food and Drug Law seminars at Boston University, University of Maryland, and University of Virginia Law Schools. She serves on the editorial boards of the *Guide to Medical Device Regulation* and the F*ood and Drug Administration Enforcement Manual* and has published a number of articles related to medical device regulation.

Linda Golodner is President of the National Consumers League, the nation's oldest consumer organization. She also chairs the National Council on Patient Information and Education and serves on the Board of Directors of the National Patient Safety Foundation, the Patient Safety Institute, and the American National Standards Institute, where she has chaired the Consumer Interest Forum. Among other activities, Ms. Golodner has served on the Steering Committee of the Centers for Education and Research on Therapeutics and the National Research Council Board on Agriculture and Natural Resources, and she is a member of the Underwriters Laboratories Consumer Advisory Council. She was appointed to the White House Apparel Industry Partnership, which she co-chaired, and she now serves on the Board of Directors of its successor organization, the Fair Labor Association. She received the American Pharmacists Association's Hugo H. Schaefer Award and has been honored by the United Nations Association (National Capitol Area) for her work in human rights.

Stephen J. Haines, M.D., is the Lyle A. French Chair and Head of the Department of Neurosurgery, University of Minnesota. He serves on the Neurological Devices Panel for the Medical Device Advisory Committee of

the FDA Office of Device Evaluation. Dr. Haines has a primary clinical interest in pediatric neurosurgery. His work focuses on the application of advanced clinical research techniques to neurosurgery and the development of resources for the evidence-based practice of neurosurgery.

Patricia Hicks, M.D., is Associate Professor in the Division of General Academic Pediatrics in the Department of Pediatrics at the University of Texas Southwestern Medical School at Dallas and Adjunct Professor of Law at Southern Methodist University. She is also the mother of a son who relies on a varying array of life-sustaining medical devices that he uses at home and at school. Dr. Hicks is the Director of the Pediatric Residency Training Program and Director of the Residents' Continuity of Care Clinic in the residency training program where she teaches residents and also cares for children with complex chronic health conditions and counsels and advises their families, schools, and community. Her teaching responsibilities include a Clinical Ethics in Medicine medical school course and a combined law school and medical school course, Law, Literature, and Medicine. As a member of the hospital's Information Systems Committee, she is involved with projects related to electronic medical records and database organization and design for research, reporting, clinical decision support, and monitoring.

Stephen W. Lagakos, Ph.D., is Chair, Department of Biostatistics, Harvard University School of Public Health. He is a member of the Institute of Medicine and recently served on the Committee to Assess the Need for Clinical Trials of Testosterone Replacement Therapy. Dr. Lagakos' current research involves a variety of statistical issues arising in clinical trials and other longitudinal studies, with particular emphasis on statistical methods and analyses relating to HIV and other infectious diseases.

George Lister, M.D., is Professor and Chairman of Pediatrics, University of Texas Southwestern Medical School. He was formerly Professor of Pediatrics and Anesthesiology and Chief, Section of Critical Care and Applied Physiology, Department of Pediatrics at Yale University School of Medicine and Lecturer in the Department of Cellular and Molecular Physiology. He was also Medical Director of Pediatric Intensive Care at the Yale-New Haven Hospital. He is past Chair of the Board of Directors of the American Board of Pediatrics, past President of the Society for Pediatric Research, and National Council Member of the American Pediatric Society. With a research focus on oxygenation and hypoxia in infants and children, Dr. Lister has chaired the NICHD Collaborative Home Infant Monitoring Evaluation study, which has examined the use of apnea monitors for children considered at risk for SIDS.

Jonathan J. Rosen, Ph.D., is a member of the Harvard Medical School faculty, a Senior Research Scientist at the Massachusetts General Hospital, and director of the research implementation program for the nonprofit Center for the Integration of Medicine and Innovative Technology (CIMIT) Consortium. He is a member of the National Academy of Engineering's Roundtable on Biomedical Engineering Materials and Applications. During his corporate career with Johnson & Johnson, he managed the cardiovascular development program, directed the corporate advanced research program for their Corporate Office of Science and Technology, and served as Chief Technical Officer for their Surgical Instrument Division before leaving to start a series of medical device ventures in Europe and in the United States. He is currently involved in several projects related to pediatric medical devices and the development of new technologies to improve care for underserved patient populations.

Index

B

C

D

E

F

G

H

I

J

L

M

N

O

P

Q

R

S

T

U