Addressing the Barriers to Pediatric Drug Development: Workshop Summary

Cori Vanchieri, Adrienne Stith Butler, and Andrea Knutsen, Rapporteurs; Forum on Drug Discovery, Development, and Translation; Institute of Medicine

ISBN: 0-309-10743-1, 64 pages, 6 x 9, (2008)

ADDRESSING THE BARRIERS TO PEDIATRIC DRUG DEVELOPMENT

Workshop Summary

Cori Vanchieri, Adrienne Stith Butler, and Andrea Knutsen, *Rapporteurs*

Forum on Drug Discovery, Development, and Translation

Board on Health Sciences Policy

INSTITUTE OF MEDICINE
OF THE NATIONAL ACADEMIES

THE NATIONAL ACADEMIES PRESS
Washington, D.C.
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.

Support for this project was provided by the Department of Health and Human Services (Contract Nos. 223-01-2460, HHSP233200600500P, HHSPP23320042509X1, and N01-OD-4-2139); the Department of Veterans Affairs (Contract No. V101(93)P-2136); Abbott Laboratories; American Diabetes Association; American Society for Microbiology; Amgen, Inc.; Association of American Medical Colleges; AstraZeneca Pharmaceuticals; Blue Cross Blue Shield Association; Burroughs Wellcome Fund; Doris Duke Charitable Foundation; Eli Lilly and Company; Entelos, Inc.; Genentech; GlaxoSmithKline; Johnson & Johnson; March of Dimes Foundation; Merck and Company; Pfizer, Inc.; Schering-Plough Research Institute; and UnitedHealth Foundation. 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 this project.

International Standard Book Number-13: 978-0-309-10742-6
International Standard Book Number-10: 0-309-10742-3

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

Suggested citation: IOM (Institute of Medicine). 2008. *Addressing the barriers to pediatric drug development: Workshop summary*. Washington, DC: The National Academies Press.

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.

"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. Charles M. Vest 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. Charles M. Vest are chair and vice chair, respectively, of the National Research Council.

www.national-academies.org

FORUM ON DRUG DISCOVERY, DEVELOPMENT, AND TRANSLATION

Gail H. Cassell (*Co-Chair*, 1/1/2005–12/31/2008), Eli Lilly and Company
Jeffrey M. Drazen (*Co-Chair*, 7/1/2008–12/31/2008; *Member*, 1/1/2005–6/30/2008), *New England Journal of Medicine*
Edward W. Holmes (*Co-Chair*, 1/1/2005–6/30/2008; *Member*, 7/1/2008–12/31/2008), National University of Singapore
Barbara M. Alving (4/10/2008–12/31/2009), National Center for Research Resources
Naomi Aronson (1/9/2007–12/31/2008), Blue Cross and Blue Shield Association
Hal Barron (8/1/2008–12/31/2008), Genentech, Inc.
Leslie Z. Benet (1/1/2005–12/31/2008), University of California, San Francisco
Nina Bhardwaj (1/1/2005–9/7/2006), New York University School of Medicine
Catherine Bonuccelli (1/9/2007–12/31/2008), AstraZeneca Pharmaceuticals
Linda Brady (1/9/2007–12/31/2008), National Institute of Mental Health
Robert M. Califf (1/1/2005–12/31/2008), Duke University Medical Center
Scott Campbell (1/1/2005–12/31/2008), American Diabetes Association
C. Thomas Caskey (1/1/2005–12/31/2008), The University of Texas-Houston Health Science Center
Francis D. Chesley, Jr. (1/9/2007–10/25/2007), Agency for Healthcare Research and Quality
Mark Clanton (1/1/2005–12/31/2006), National Cancer Institute
Peter Corr (1/9/2007–12/31/2008), Celtic Therapeutics
James H. Doroshow (7/19/2007–12/31/2008), National Cancer Institute
William E. Evans (1/1/2005–12/31/2006), St. Jude Children's Research Hospital
Joseph M. Feczko (1/9/2007–12/31/2008), Pfizer, Inc.
Wayne Fenton [Deceased] (1/1/2005–9/3/2006), National Institute of Mental Health
Garret A. FitzGerald (1/1/2005–12/31/2008), University of Pennsylvania School of Medicine
Elaine K. Gallin (1/1/2005–12/31/2008), The Doris Duke Charitable Foundation
Steven K. Galson (1/9/2007–12/31/2008), Office of the Surgeon General

Alan M. Garber (1/1/2005–12/31/2007), Stanford University
Robert L. Garnick (11/16/2007–2/28/2008), Genentech, Inc.
Mikhail Gishizky (1/1/2005–12/31/2008), Entelos, Inc.
Stephen Groft (1/1/2005–12/31/2008), National Institutes of Health
Carole A. Heilman (1/1/2005–3/13/2006), National Institute of Allergy and Infectious Diseases
Peter K. Honig (7/19/2007–12/31/2008), Merck & Co., Inc.
Dale Hu (1/1/2005–12/31/2005), Centers for Disease Control and Prevention
Richard A. Justman (7/19/2007–12/31/2008), United HealthGroup
Michael Katz (1/1/2005–12/31/2008), March of Dimes Foundation
William F. Keane (1/1/2005–7/3/2007), Merck & Co., Inc.
Chaitan Khosla (1/1/2005–12/31/2006), Stanford University
Antonia Kolokathis (1/1/2005–12/31/2005), Pfizer, Inc.
Allan M. Korn (1/1/2005–12/31/2006), Blue Cross and Blue Shield Association
David Korn (1/1/2005–12/31/2008), Association of American Medical Colleges
Ronald L. Krall (1/9/2007–12/31/2008), GlaxoSmithKline
Jeffrey M. Leiden (1/1/2005–12/31/2007), Clarus Ventures
John M. Leonard (1/9/2007–7/5/2007), Abbott Laboratories
Nancy Loving (1/1/2005–6/7/2006), National Coalition for Women with Heart Disease
John R. Marler (1/1/2005–12/31/2008), National Institute of Neurological Disorders and Stroke
Musa Mayer (1/1/2005–12/31/2008), AdvancedBC.org
Mark B. McClellan (4/2/2007–12/31/2008), The Brookings Institution
Garry A. Neil (1/1/2005–3/19/2007), Johnson & Johnson
Joshua J. Ofman (1/1/2005–12/31/2008), Amgen, Inc.
Suzanne R. Pattee (1/1/2005–12/31/2008), Cystic Fibrosis Foundation
Cecil B. Pickett (1/1/2005–12/31/2006), Schering-Plough Research Institute
Joanne L. Rhoads (1/9/2007–12/31/2008), National Institute of Allergy and Infectious Diseases [Retired]
Todd Rich (3/2/2008–12/31/2008), Genentech, Inc.
Brian Schuster (1/1/2005–12/31/2006), U.S. Department of Veterans Affairs
B. A. Schwetz (1/1/2005–9/30/2007), U.S. Department of Health and Human Services
Janet Shoemaker (1/1/2005–12/31/2008), American Society for Microbiology
Lana Skirboll (1/9/2007–12/31/2008), National Institutes of Health
Nancy S. Sung (1/1/2005–12/31/2008), Burroughs Wellcome Fund

James R. Swartz (1/1/2005–12/31/2005), Stanford University
Jorge A. Tavel (7/19/2007–12/31/2008), National Institute of Allergy and Infectious Diseases
Reed V. Tuckson (1/1/2005–7/3/2007), UnitedHealth Group
Sean Tunis (1/1/2005–12/31/2006), Centers for Medicare & Medicaid Services
Janet Woodcock (1/1/2005–12/31/2008), U.S. Food and Drug Administration

IOM Stafff

Robert B. Giffin (*Director*, 7/13/2006–present)
Alexander K. Ommaya (*Director*, 1/1/2005–7/7/2006)
Adrienne Stith Butler (*Senior Program Officer*, 12/1/2006–5/31/2007)
Sally Robinson (*Program Officer*, 12/18/2006–present)
Heather Begg (*Program Associate*, 1/1/2005–7/7/2006)
Andrea Knutsen (*Senior Program Assistant*, 10/3/2005–present)
Jennifer Rainey (*Research Assistant*, 1/1/2005–7/7/2006)

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 report 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:

Marion E. Broome, Indiana University School of Nursing and *Nursing Outlook* Journal
P. Joan Chesney, St. Jude Children's Research Hospital
Thomas G. Dewitt, Cincinnati Children's Hospital Medical Center
William E. Evans, St. Jude Children's Research Hospital
Michael Katz, March of Dimes Birth Defects Foundation
John S. March, Department of Psychiatry and Behavioral Science, Duke University

Although the reviewers listed above have provided many constructive comments and suggestions, they did not see the final draft of the report before its release. The review of this report was overseen

by **Dr. Ralph E. Kauffman,** Professor Emeritus, University of Missouri-Kansas City. Appointed by the Institute of Medicine, he was responsible for making certain that an independent examination of this report was carried out in accordance with 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

Summary[1]

Decades of research have demonstrated that children do not respond to medications in the same way as adults. Differences between children and adults in the metabolism, renal clearance, other drug disposition mechanisms, and overall response to medications are due to profound anatomical, physiological, and developmental differences. Substantial variation also exists among children of different ages in the ability to metabolize, absorb, excrete, and transform medications. Although few would argue that children should receive medications that have not been adequately tested for safety and efficacy, the majority of drugs prescribed for children—50 to 75 percent—have not been tested in pediatric populations. The younger the age group, the less information is available.

Product labels provide important information to clinicians and consumers on the risks and appropriate use of drugs, and are based on the results of controlled clinical studies. The limited amount of testing of drugs in pediatric patients is reflected in the lack of pediatric-specific information on the product labels for many drugs used to treat children. Without adequate data from such testing, prescribing drugs appropriately becomes challenging for clinicians treating children, from infancy through adolescence.

Current laws employ both incentives and mandates to spur drug makers to test their products in pediatric populations and to enhance the

[1]The Forum's role was limited to planning the workshop, and the workshop summary has been prepared by the workshop rapporteurs as a factual summary of what occurred at the workshop.

pediatric information provided on drug labels. The result has been a substantial increase in pediatric drug trials, with corresponding information being added to the labels for 115 drugs. Nonetheless, a pressing need for more study remains. Although incentives exist for the study of new, on-patent drugs, some argue that additional incentives are needed, especially to encourage testing of older, off-patent drugs. The two existing laws that address the need to study drugs in pediatric populations—the Best Pharmaceuticals for Children Act (BPCA)[2] and the Pediatric Research Equity Act (PREA)[3]—will sunset in October 2007 without congressional action.[4]

In this context, and given the urgency of addressing the current gap in pediatric drug safety, the Institute of Medicine's Forum on Drug Discovery, Development, and Translation held a 1-day workshop, *Addressing the Barriers to Pediatric Drug Development,* on June 13, 2006. The purpose of the workshop was to identify barriers to the development and testing of drugs for pediatric populations, as well as ways in which the system can be improved to facilitate better treatments for children. The Forum invited representatives from the U.S. Food and Drug Administration (FDA), the National Institutes of Health, the American Academy of Pediatrics, the pharmaceutical industry, academia, and several patient advocacy groups to discuss

- the current regulatory framework,
- current challenges in prescribing and developing drugs for children,
- models for enhancing pediatric drug development, and
- challenges and opportunities for the future.

REGULATORY FRAMEWORK

Regulatory efforts to protect children from harmful medications began in the early part of the twentieth century. Many of the initial laws were established in response to specific incidents involving products that caused harm, especially to children; according to Dr. Lisa Mathis of the FDA, however, the resulting laws benefited adults disproportionately. Information on the use of drugs in children was limited and remained insufficient for decades.

[2]*Best Pharmaceuticals for Children Act*. Public Law 107–109. http://www.fda.gov/opacom/laws/pharmkids/pharmkids.html (2002).

[3]*Pediatric Research Equity Act*. Public Law 108–155. http://frwebgate.access.gpo.gov/cgi-bin/getdoc.cgi?dbname=108_cong_public_laws&docid=f:publ155.108 (2003).

[4]Subsequent to this workshop, both BPCA and PREA were reauthorized by Congress as part of the Food and Drug Administration Amendments Act of 2007, Public Law 110-85, which was signed by the President in September 2007.

Workshop participants gave an overview of the current regulatory framework for pediatric drug development and testing. BPCA, passed in 2002, provides 6 months of additional marketing exclusivity and patent protection when studies are performed in children as requested by the FDA. The act also specifies a process by which the FDA can request studies of older, off-patent drugs. PREA was passed in 2003 as a complement to the incentives offered by BPCA. Under this act, the FDA can require pediatric studies of a product for which a New Drug Application is submitted if the agency determines the product is likely to be used in a substantial number of pediatric patients or would provide meaningful benefits for children over existing treatments.

Workshop participants described the positive impact of these laws on the development of therapies for children. Since 2002, in addition to the labeling changes for 115 pediatric drugs noted above, 12 new pediatric formulations and 8 extemporaneous formulations have been devised; in addition, adverse events have been reported for 54 pediatric drugs. Yet many participants agreed that, while the incentives and mandates in these laws are working, more could be done. Suggestions included adding a requirement to new iterations of BPCA and PREA that product labels provide information on the results of pediatric trials regardless of the product's approval status, and securing additional funding for studies of off-patent, older agents, as the Foundation for the National Institutes of Health lacks sufficient resources to conduct the needed pediatric studies of these drugs.

CURRENT CHALLENGES IN DEVELOPING AND PRESCRIBING DRUGS FOR CHILDREN

Challenges in developing and prescribing pediatric drugs were a central theme of the workshop. Barriers to the development of medications for children were discussed, including ethical, economic, logistical and technical barriers, as well as the industry perspective of these barriers. Ethical barriers cited include clinicians who prescribe drugs off label absent sufficient pediatric data, which results in delays in needed research; drug sponsors who pursue pediatric clinical trials late in a drug's life cycle, with more objectives and procedures included than may be appropriate for the study design; academic institutions that fail to reward investigators for participating in clinical trials; and a clinical research enterprise that lacks transparency at all levels. An additional barrier is a reluctance to alter existing practices and focus on the goal of finding efficient and effective ways to develop adequately studied drugs for the treatment of children.

Economic barriers were outlined as well. One such barrier is the dif-

ficulty of stimulating investment in pediatric drugs by pharmaceutical companies. For one thing, the market is relatively small, thereby reducing financial incentives. For another, pediatric trials involve many special considerations relative to adult studies. For example, different endpoints may be required; the volume of samples that can be taken may necessitate a more innovative statistical design or require multisite or even global studies to accrue sufficient patients; and additional safety concerns must be taken into account, such as issues of growth and development.

Logistical and technical barriers also exist. They include a deficient U.S. infrastructure for pediatric drug studies, limited availability of baseline information on frequency of disease and treatments of choice, and a lack of accepted endpoints and validated pediatric assessment tools.

Participants also described problems with drug formulations that are not suitable for children and with extemporaneous formulations that may be unsafe because of a lack of quality control. They also discussed dosing issues, including imprecise measuring instruments, problems with taste and palatability (which can affect adherence), and the need for alternatives to oral liquid formulations. In addition, participants emphasized the lack of information noted above, and suggested that moving from dose guessing to informed prescribing will require additional study. Also stressed was the need to improve the dissemination of information to physicians so they can make the best choices in prescribing medications for individual pediatric patients.

MODELS FOR ENHANCING PEDIATRIC DRUG DEVELOPMENT

Workshop participants cited creative solutions from the vaccine development arena that might be applied to pediatric drugs: the no-fault compensation system for patients (or their families) who suffer serious adverse reactions from required childhood vaccines, and the two-page public information fact sheets on each vaccine. Participants were also encouraged by promising regulatory approaches that have been adopted by the European Union and appear to be more cohesive than current U.S. regulations. These include a new Pediatric Committee working at the European Agency for the Evaluation of Medicinal Products; new incentives for patent-protected and off-patent medicinal products; and the Pediatric Investigation Plan, a document describing proposed studies of a drug in pediatric populations, which must be approved by the Pediatric Committee if the associated incentives are to be received. Also discussed was a model used by St. Jude Children's Research Hospital to develop innovative public–private partnerships for the production of new molecularly targeted drugs for pediatric oncology patients.

CHALLENGES AND OPPORTUNITIES FOR THE FUTURE

Workshop participants suggested many critical needs and opportunities for further progress, addressing both systemic solutions and potential means of eliminating the economic barriers discussed previously. Suggestions included

- improving the postmarket safety surveillance system;
- combining incentives and requirements for the conduct of pediatric research into one process;
- increasing transparency throughout the clinical research enterprise;
- increasing training for the next generation of clinical pharmacologists and pediatric researchers;
- exploring practice-based research networks to expand the pool of pediatric patients;
- providing additional funding and incentives for pediatric drug development; and
- implementing lessons learned from models such as U.S. vaccine development, European Union regulations, and St. Jude's efforts to develop public–private partnerships for the discovery and development of pediatric cancer drugs.

1

Introduction

Decades of research have demonstrated that children do not respond to medications in the same way as adults. Although few would argue that children should receive medications that have not been adequately tested for safety and efficacy, the majority of drugs prescribed for children—50 to 75 percent—have not been tested in pediatric populations (Budetti, 2003; Roberts et al., 2003; FDA, 2006). Without adequate data from such testing, prescribing drugs appropriately becomes challenging for clinicians treating children, from infancy through adolescence. The Institute of Medicine's Forum on Drug Discovery, Development, and Translation held a 1-day workshop, *Addressing the Barriers to Pediatric Drug Development,* on June 13, 2006, to identify barriers to the development and testing of drugs for pediatric populations, as well as to examine ways in which the system can be improved to facilitate better treatments for children. Participants included representatives from the U.S. Food and Drug Administration (FDA), the National Institutes of Health, the American Academy of Pediatrics, the pharmaceutical industry, academia, and several patient advocacy groups.

RESPONSE TO DRUGS IN VARIOUS AGE GROUPS

Differences between children and adults in the metabolism, renal clearance, other drug disposition mechanisms, and overall response to medications are due to profound anatomical, physiological, and developmental differences (Kearns et al., 2003; McKinney, 2003). Substantial varia-

tion also exists among children of different ages in their ability to metabolize, absorb, excrete, and transform medications (ICH, 2000; Roberts et al., 2003). As noted above, however, minimal information is available on the safety and efficacy of drugs in pediatric patients, and the younger the age group, the more likely this is to be the case (Roberts et al., 2003).

Recent studies of medications for pediatric patients have revealed several unsuspected differences in efficacy by age group. For example, a study by the Pediatric AIDS Clinical Trials Group compared combinations of drugs for treating children with HIV. Results indicated that a regimen of two daily doses of nelfinavir (Viracept) was pharmacokinetically superior to three daily doses, particularly in smaller, younger children. These were unexpected and positive findings for clinicians attempting to increase medication adherence and reduce the development of drug resistance (Floren et al., 2003; McKinney, 2003).

PRODUCT LABELING

Because most drugs prescribed for children have not been tested in pediatric populations, important information on their risks and appropriate use for these patients is not available on the product labels. These labels provide health care professionals with details on the use of the drugs, including information from carefully controlled clinical studies. Poor labeling is often an indicator of inadequate study. Off-label use occurs when drugs are prescribed for purposes other than those included under the terms of the FDA product approval (Roberts et al., 2003). Off-label use of drugs is common in adults but far more prevalent in children. While such use can be beneficial to the patient, it can also result in adverse reactions due to a lack of understanding of the drug's pharmacokinetics in this population.

Current laws employ both incentives and mandates to encourage drug makers to test their products in pediatric populations and to enhance the pediatric information provided on drug labels. The result has been a substantial increase in pediatric drug trials, with corresponding information being added to the labels for 115 drugs. Examples of drugs for which labeling changes have affected dosing and risk include loratadine (Claritin) and fluvoxamine maleate (Luvox). In a single-dose pharmacokinetic study of pediatric subjects (age 2 to 5 years) it was found that children receiving a 5-mL dose of CLARITIN Syrup containing 5 mg of loratadine had comparable range of pharmacokinetic parameters (AUC and Cmax) to adults and older children who had received a tablet or syrup containing 10 mg of loratadine. Likewise, fluvoxamine maleate, used to treat obsessive-compulsive disorder, was found to be most effective in adolescents at the recommended adult dose, but girls aged 8 to 11

were found to need a smaller dose (approximately half the values seen in the male patients) (Roberts et al., 2003).[1]

Despite increases in the testing of drugs in pediatric populations, a pressing need for more study remains. Although incentives exist to study new, on-patent drugs, some argue that additional incentives are needed, especially to encourage testing of older drugs that are off-patent. The two existing laws that address the need to study drugs in pediatric populations—the Best Pharmaceuticals for Children Act (BPCA) and the Pediatric Research Equity Act (PREA)—will sunset in October 2007 without congressional action.[2]

ORGANIZATION OF THIS SUMMARY

The following chapters summarize the presentations and discussions at the workshop. Chapter 2 reviews the regulatory framework for pediatric drug development and testing, summarizing BPCA and PREA and their impact. Chapter 3 addresses challenges to the development of drugs for children, including the barriers posed by ethical concerns, economic obstacles, and logistical and technical issues; the difficulty of devising appropriate formulations; and issues of dosing, bioavailability, and drug response. Chapter 4 considers the potential adaptation of existing models—such as vaccine development, European regulatory models, and the approach used by St. Jude Children's Research Hospital to develop oncology drugs—to enhance pediatric drug development. The final chapter summarizes participants' suggestions for solutions and next steps.

[1]Fluvoxamine dosing was not based on body-weight. After the starting dose of 25 mg, the fluvoxamine dosing was titrated according to clinical response and tolerance, and the resulting fluvoxamine dose was in a range of 50–200 mg/day (on a bid schedule) in a 10-week study. In a pharmacokinetic study, consistent with clinical observations, fluvoxamine exposure (AUC and Cmax at steady state) was significantly higher in younger female patients compared to those in the corresponding age group of male patients. Hence, the label says that therapeutic effects in female children may be achieved with lower doses.

[2]Subsequent to this workshop, both BPCA and PREA were reauthorized by Congress as part of the Food and Drug Administration Amendments Act of 2007, Public Law 110-85, which was signed by the President in September 2007.

2

Regulatory Framework

Regulatory efforts to protect children from harmful medications began in the early part of the 20th century. Many of the initial laws were established in response to specific incidents involving products that caused harm. Dr. Lisa Mathis, Acting Director, Division of Pediatric Drug Development, U.S. Food and Drug Administration (FDA), reviewed this history (summarized in Box 2-1).

The Biologics Control Act of 1902 was passed after a diphtheria antitoxin was contaminated with tetanus spores, killing 13 children in St. Louis, Missouri. The Pure Food and Drug Act followed in 1906. This law, which prohibited the manufacture, sale, or transport of adulterated or misbranded drugs, was passed in response to deaths among patients due to medications containing dangerous substances. For example, Mrs. Winslow's Soothing Syrup (used for teething) contained high amounts of alcohol and morphine, which led to coma, addiction, and death among infants.

In 1938, the Food, Drug, and Cosmetic Act was passed. This act gave the FDA authority to oversee the safety of food, drugs, and cosmetics. Its introduction was influenced by 107 deaths, many among children, reported to be caused by the ingestion of Elixir Sulfanilamide, used to treat infections, which contained diethylene glycol, a solvent in antifreeze that is toxic to the kidneys. The act required drug firms to prove to the FDA that any new drug was safe before it could be marketed. The 1962 Kefauver-Harris Amendment was a response to the thalidomide tragedy;

BOX 2-1 Benchmarks in the Regulation of Pediatric Drugs

1902 Biologics Control Act
1906 Pure Food and Drug Act
1938 Food, Drug, and Cosmetic Act
1962 Kefauver-Harris Amendment
1979 labeling requirement
1994 Pediatric Labeling Rule
1997 Food and Drug Administration Modernization Act (FDAMA)
1998 Pediatric Rule*
2002 Best Pharmaceuticals for Children Act (BPCA)
2003 Pediatric Research Equity Act (PREA)

*The Pediatric Rule was enjoined, or prohibited, in 2002 by a federal court, which ruled that Congress had not given the FDA authority to require extensive testing of drugs for children (*Association of American Physicians and Surgeons, Inc.* v. *U.S. Food and Drug Administration*, 226 F Supp 2d 204 [DC Cir 2002]).
SOURCE: Mathis, 2006.

thalidomide, a sleeping pill, caused severe birth defects in the offspring of European women who took it, as well as women in the United States who gained access to it as an investigational new drug. Before the amendment was passed, an FDA New Drug Application had to demonstrate only that the drug was safe. Under the amendment, an FDA New Drug Application was required to demonstrate that the drug was effective as well as safe.

Many of the incidents that inspired the above legislation involved children, but according to Dr. Mathis, the resulting laws benefited adults disproportionately. Information on the use of drugs in children was limited and remained insufficient for decades. Then in 1979, the FDA issued a requirement that labels note specifically whether safety and efficacy had been established in pediatric populations. The 1994 Pediatric Labeling Rule, another FDA regulation, requested that the pharmaceutical industry submit literature and other data providing additional information on the use of drugs in pediatric patients. However, it proved relatively ineffective. In 1997, the Food and Drug Administration Modernization Act (FDAMA) provided incentives for companies to test drugs in pediatric populations voluntarily: 6 months of additional marketing exclusivity and patent protection when studies are performed in children as

requested by the FDA.[1] The patent exclusivity of FDAMA was extended through 2007 with the Best Pharmaceuticals for Children Act (BPCA), passed in 2002. As a complement to the incentives offered by BPCA, the Pediatric Research Equity Act (PREA), passed in 2003, imposed a requirement that pharmaceutical companies test in a pediatric population a new drug likely to be used in children.

BEST PHARMACEUTICALS FOR CHILDREN ACT[2]

The Best Pharmaceuticals for Children Act signed into law January 4, 2002, established a process for the study of on-patent and off-patent drugs for use in pediatric populations, addressing collaboration on scientific investigation, clinical study design, weight of evidence, and ethical and labeling issues. As noted above, BPCA also renewed FDAMA's 6 months of marketing and patent protection for drugs whose sponsors perform the studies and produce the reports requested by the act. This 6-month extension is offered not only for a drug that was studied in pediatric populations, but also for any of the company's formulations, dosage forms, and indications that contain the same active part, or moiety, of a molecule and have existing marketing exclusivity or patent life. For example, if a company markets an oral formulation and a topical cream containing the same moiety but submits a pediatric study for only one of the formulations, the 6 months of marketing exclusivity is added to patent protection for both products.

For the study of a drug that is still on patent, a company will typically submit a Proposed Pediatric Study Request to the FDA. The FDA will determine whether there is a public health benefit to support pediatric studies. BPCA also allows the FDA to initiate a study through a Written Request. If the FDA issues such a request, the drug's sponsor has 180 days to respond. If the sponsor decides to conduct the study, results are submitted to the FDA. If the sponsor does not conduct the requested study, a process is in place by which the FDA can refer on-patent products to the Foundation for the National Institutes of Health (FNIH), which works to advance research by linking private-sector donors and partners to National Institutes of Health (NIH) programs. FNIH will either fund the study or, if it lacks sufficient funding, refer the drug to NIH. If funding

[1]A patent protects a company's investment by giving it the sole right to sell a drug while the patent is in effect. When the patent expires, other companies can apply to the FDA to sell generic versions of the drug without having to repeat the original developer's clinical trials.

[2]This section is based on the presentation of Dr. Mathis.

is available, NIH will issue a Request for Proposals from third parties to conduct the needed studies.

Incentives under BPCA do not apply to biologic, generic, or off-patent drugs, or to other drugs that lack marketing exclusivity or patent protection. For those products, BPCA provides a contract mechanism through which NIH can fund pediatric studies (again contingent on available funding). NIH publishes in the *Federal Register* a list of drugs for which additional pediatric studies are needed. The list is compiled by a consensus group of representatives from the National Institute of Child Health and Human Development, the FDA, and others. The FDA issues a Written Request for the needed studies, and a product's sponsor has 30 days to respond. If the sponsor agrees to conduct the study, its results are submitted to the FDA. If not, the FDA refers the Written Request to NIH. As described above for on-patent drugs, NIH issues a Request for Proposals and awards a contract on a competitive basis to a third-party investigator. Since BPCA went into effect, the FDA has issued 11 Written Requests for studies of off-patent drugs, and NIH has published 4 Requests for Proposals (FDA, 2006).

In deciding whether to issue a Written Request for a pediatric study of an on-patent or off-patent drug, the FDA considers several factors:

- **Public health benefit.** How would studying the drug benefit pediatric populations? Is the condition it treats serious or life-threatening? Is it common? Are other therapeutic options approved for this indication, and are they labeled for use in children? How often is the drug used off-label in pediatric populations?
- **Existing information.** Are there safety signals for the drug from animal studies, from adult trials, or from spontaneous reports? Do enough safety data exist to start clinical trials in pediatric patients? (Frequently, animal data or even Phase I results for adults are inadequate to support the initiation of pediatric studies.) What is the appropriate risk–benefit balance? (The FDA would be unlikely to study a drug in pediatric patients that has resulted in many adverse events or has low efficacy in adults unless the disease treated by the drug is life-threatening. For example, the FDA would be more likely to accept adverse events for an oncology drug than for a treatment for otitis media or some other non-life-threatening disease.)
- **Needed information.** For what age groups is information needed? What studies are required to obtain the information? Are there other ways to obtain the information? Can information for pediatric populations lacking on the drug's label be extrapolated from efficacy data derived from adult studies?

TABLE 2-1 Pediatric Exclusivity Statistics (as of April 2006)

Proposed Pediatric Study Requests	465
Written Requests issued	317
Drugs granted exclusivity	118
Label changes	115
Patients in requested studies	44,763+

SOURCE: Mathis, 2006.

The Best Pharmaceuticals for Children Act mandates review of adverse events for 1 year after exclusivity for pediatric use is granted for a drug. Events are reported to the FDA's Pediatric Review Committee. The results of these reviews have led the FDA to provide more information on the drug label—including negative or uncertain results—to help guide practitioners in their use of drugs in pediatric patients. According to Dr. Mathis, another important benefit of BPCA is that study results are now posted on the FDA website.

The pediatric exclusivity provision of BPCA has done more to spur pediatric studies than any other regulatory or legislative initiative to date (FDA, 2006). As of April 2006, the FDA had received 465 Proposed Pediatric Study Requests and issued 317 Written Requests (see Table 2-1). The FDA has granted exclusivity for 118 drugs or active parts and made 115 label changes to include pediatric information.

PEDIATRIC RESEARCH EQUITY ACT[3]

The Pediatric Research Equity Act amends the federal Food, Drug, and Cosmetic Act to authorize the FDA to require pediatric studies of drugs or biologics when other approaches are insufficient to ensure that the products are safe and effective for use in children. Under PREA, the FDA can require pediatric studies of a product for which a New Drug Application is submitted if the agency determines the product is likely to be used in a substantial number of pediatric patients, or if it would provide meaningful benefits for children over existing treatments. Dr. Mathis suggested that product development programs should include pediatric studies when use of a product in children is anticipated, although efforts to support pediatric use should not delay or block access to medications for adults. Companies, regulatory authorities, health professionals, and

[3]This section is based on the presentation of Dr. Mathis.

society as a whole share responsibility for obtaining needed information on the appropriate use of medications in children.

PREA restores some important aspects of the Pediatric Rule, which was enjoined in 2002 (see Box 2-1). Unlike BPCA, under which the FDA can issue a Written Request for any indication, PREA restricts the FDA to the specific indication contained in the submission to the agency (see Table 2-2 for a comparison of BPCA and PREA). However, PREA applies to any application for a new ingredient, new indication, new dosage form, new dosage regimen, or new route of administration. In addition, while the results of BPCA-initiated studies are disseminated publicly through the FDA's website, PREA information is not routinely released to the public.

Under PREA, a pediatric assessment is required for new applications, except when waived or deferred, and is designed to provide data needed to evaluate the safety and efficacy of a drug or biologic and to support dosing and administration for each pediatric subpopulation for which the product has been found safe and effective. A waiver to the requirement for a pediatric assessment is granted when the necessary studies are impossible or highly impractical, when there is strong evidence suggesting the product would be ineffective or unsafe, or when the product does not represent a meaningful therapeutic benefit over existing therapies and is unlikely to be used in a substantial number of pediatric patients. Partial waivers may also be granted for a specific pediatric subpopulation (for example, adolescents or neonates). A partial waiver may be granted as well if a product's specific formulation cannot be effectively altered. For example, if the chemical properties of a medication prevent its production as a liquid, it may be waived from study in newborns or children under 5 years of age, who would require a liquid formulation.

TABLE 2-2 Best Pharmaceuticals for Children Act Versus Pediatric Research Equity Act

BPCA	PREA
Studies are voluntary	Studies are required
Includes orphan drugs	Orphan drugs and indications are designated exempt
Covers drugs only	Covers biologics and drugs
Studies encompass whole moiety (active part)	Studies limited to drug/indication under development
Summaries posted on FDA website	Summaries not made available publicly

SOURCE: Mathis, 2006.

IMPACT OF PEDIATRIC DRUG LEGISLATION[4]

Dr. Rodriguez provided an overview of the advancements made in the field of pediatric medicine as a result of recent legislation. These advancements include improvement in product labeling, increased identification of adverse events, and development of new pediatric formulations. For example, in about one-fifth of the drugs studied since passage of the legislation, clearance, or the body's efficiency in eliminating a drug, has been found to be different in young populations than was previously assumed. Completed studies have made clear that effects on growth and behavior need to be examined in pediatric trials.

Under FDAMA, important dosing changes and safety information have been added to drug labels to indicate how these drugs can be prescribed more appropriately for pediatric populations (Roberts et al., 2003). Because new studies have been conducted, some labels now indicate that certain drugs can be used in younger children. Twelve new pediatric formulations—for analgesia, HIV, allergic rhinitis, influenza, and other conditions (see Table 2-3)—and eight extemporaneous formulations (see Table 2-4) have been devised since BPCA was enacted.

The following are some examples of labeling changes that have impacted dosing or age of administration or provided warning of potential adverse events; none of these findings would be known without the associated pediatric initiative:

- Fluoxetine (Prozac) underwent major labeling changes after a 19-week clinical pediatric trial of its use for major depressive disorder in patients aged 8 to 17 and obsessive-compulsive disorder in patients aged 7 to 17 found that those taking the drug experienced more limited growth than those not taking it. The label now warns physicians to monitor the height and weight of pediatric patients treated with fluoxetine.
- Gabapentin (Neurontin), a drug used for seizures in children, underwent labeling changes after pediatric studies demonstrated that higher doses were required to control seizures in those younger than age 5 (on a per-kilogram basis, patients younger than 5 years appear to clear the drug more quickly than adult patients and therefore require higher doses for the drug to be effective). In addition, new adverse events (for example, aggression and hostility) were identified in children younger than age 12.
- Labeling changes were made to betamethasone, a corticosteroid used in several common, over-the-counter topical creams for jock itch

[4]This section is based on the presentation of Dr. William Rodriguez, Science Director for Pediatrics, Office of New Drugs, FDA.

TABLE 2-3 New Product Pediatric Formulations

Product	Exclusivity Granted	Labeled
Midazolam (Versed), Roche	9/18/1998	10/15/1998
Abacavir (Ziagen), GlaxoSmithKline	12/14/1998	12/17/1998
Atovaquone/proguanil (Malarone), GlaxoSmithKline	7/14/1998	12/2/2003
Ibuprofen/pseudoephedrine suspension (Children's Motrin Cold), McNeil		8/1/2000
Gabapentin (Neurontin), Parke-Davis	2/2/2000	10/12/2000
Oseltamivir (Tamiflu), Roche	3/22/2004	12/14/2000; 6/24/2004
Ribavirin (Rebetol), Schering-Plough	5/9/2001	12/28/2001; 7/29/2003
Ibuprofen/pseudoephedrine suspension (Children's Advil Cold), Whitehall	9/19/2001	4/18/2002
Montelukast (Singulair), Merck	12/10/2001	7/26/2002
Nizatidine (Axid), Reliant		5/25/2004
Desloratidine (Clarinex), Schering-Plough	2/18/2008	9/1/2004
Emtricitabine (Emtriva), Gilead Sciences		9/28/2005

SOURCE: Rodriguez, 2006.

TABLE 2-4 Pediatric Extemporaneous Formulations*

Product	Exclusivity Granted	Labeled
Sotalol (Betapace), Berlex	1/6/2000	10/1/2001
Linosipril (Prinivil), Merck	11/19/2001	5/29/2003
Enalapril (Vasotec), Merck	2/22/2000	2/13/2001
Linisipril (Zestril), AstraZeneca	11/9/2001	7/1/2003
Fosinopril (Monopril), Bristol-Myers	1/27/2003	5/27/2003
Benazepril (Lotensin), Novartis	7/2/2003	3/23/2004
Losartan (Cozar), Merck	3/20/2002	3/11/2004
Amlodipine (Norvasc), Pfizer	11/27/2001	1/8/2004

*An extemporaneous formulation is a pharmaceutical product that has been freshly compounded without prior preparation or in an improvised manner. This is often done because the concentration of the product needs to be individualized.
SOURCE: Rodriguez, 2006.

or athlete's foot (Lotrisone, Diprolene, Diprosone), after studies showed hypopituitary–adrenal axis suppression in children under age 12. The label now indicates that the creams should not be used in this age group.

- The labels for two anesthetic agents—propofol (Diprivan) and sevoflurane (Ultane)—were changed after studies identified new adverse

events. Propofol is used for induction and/or maintenance of anesthesia. The drug was associated with increased mortality relative to standard sedative agents when used in pediatric intensive care units (9 percent versus 4 percent). Serious bradycardia occurred when propofol was administered concomitantly with fentanyl. Similarly, sevoflurane, also used for induction and maintenance of general anesthesia, was found to cause rare cases of seizure in children without a previous seizure history. Seizures can occur immediately or up to 24 hours after the therapy is stopped. This information is now on the label for these drugs.

- Etodolac (Lodine), used for symptom relief in juvenile rheumatoid arthritis, underwent labeling changes after studies showed that patients aged 6 to 16 years required a higher dose (on a per-kilogram basis) than expected—approximately twice the lower dose recommended for effective treatment in adults.
- Labeling changes were made to fluvoxamine (Luvox), a treatment for obsessive-compulsive disorder, to recommend higher doses in adolescents than were previously indicated, with the exception of girls aged 8 to 11, who may require lower doses because the drug can make them drowsy.

In addition to labeling changes, pediatric studies have revealed important information about adverse drug events. As noted earlier, in 2003, BPCA began mandating adverse event reporting for 1 year after pediatric exclusivity is granted. Since then, adverse events have been reported for 54 drugs. These reports include suicidal ideation in patients taking selective serotonin reuptake inhibitors (SSRIs) and ribavirin (Rebetol)–interferon alfa-2b, recombinant (Intron A), as well as suppression of linear growth in children taking fluoxetine (Prozac) and systemic corticosteroids. In addition, accidental exposures to and misuse or abuse of the fentanyl transdermal system (Duragesic) have been revealed: between 1990 and 2003, four pediatric deaths were reported; during the year of mandatory reporting, five pediatric deaths were reported.

In concluding, Dr. Rodriguez summarized the major impacts of the study of drugs under BPCA and PREA. First, recent legislation is having a positive impact on the development of therapies for children. Second, children have been found to be more physiologically dynamic and variable than was previously thought. Finally, Dr. Rodriguez suggested that defining endpoints and validating assessment tools are of critical importance for the study of the use of drugs in pediatric populations.

DISCUSSION

Workshop participants seconded Dr. Rodriguez's view that the current legislation is having a positive impact on the development of therapies for children. Dr. Dianne Murphy, Director, Office of Pediatric Therapeutics, FDA, and several other participants suggested that in the new iterations of BPCA and PREA, a requirement be included that product labels provide information on results of pediatric trials regardless of the product's approval status and the process. For off-patent, older agents, FNIH lacks sufficient resources to conduct the needed pediatric studies. Dr. Wayne Snodgrass, Chairman of the Committee on Drugs, American Academy of Pediatrics, cited morphine as an example. Information is lacking on the optimal use of morphine, or even on the drug's basic kinetics, in various age groups and with different disease processes.

3

Current Challenges in Developing and Prescribing Drugs for Children

Workshop participants described several barriers to the development of drugs for pediatric populations, including ethical concerns, economic barriers, and logistical and technical issues. The industry perspective on these barriers was discussed as well. Participants also described several challenges in using drugs to treat children—problems with formulations and issues of dosing, bioavailability, and drug response.

BARRIERS TO PEDIATRIC DRUG DEVELOPMENT

Barriers to pediatric drug development identified by workshop participants include ethical concerns, economic barriers, and logistical and technical issues. Delays in pediatric drug testing that result from these barriers have led to unnecessary exposure to ineffective drugs or ineffective dosing of effective drugs, both of which prevent patients from receiving appropriate therapies. Dr. Murphy noted that, absent the results of pediatric drug testing, it is impossible to know whether a drug found effective for adults will work well in children, or might work in children if the dose were adjusted. Without pediatric testing and long-term surveillance, it is also impossible to know what safety signals to watch for and how to manage them, and adverse events that might be unique to pediatric populations remain unknown.

Ethical Concerns[1]

According to Dr. Nelson, ethical concerns should not be a barrier to pediatric research. Although children cannot consent to participate in research studies, there is broad international agreement on three core ethical principles that should guide pediatric research:

- Children should not be enrolled in research unless necessary to answer an important scientific question about the health and welfare of children.
- Research involving children must be characterized by a balance of risks and potential benefits comparable to that of available alternatives.
- Research offering no direct benefit to children must be restricted to that posing minimal risk.

Although definitions of "minimal risk" and "low risk" vary, Dr. Nelson argued that the differences are insignificant. For research with the prospect of direct benefit to the study population, every health authority uses similar language. The pertinent U.S. Food and Drug Administration (FDA) language appears in Subpart D of the Code of Federal Regulations, "Additional Safeguards for Children Involved in Clinical Investigations" (21 CFR §50.52). This language suggests that risks must be justified by anticipated benefits, and anticipated benefits and risks must be balanced in both arms of a study. The variability seen in Institutional Review Board (IRB) determinations is not driven by differences in definitions, but by the inevitable differences in individual judgments within any group of people (Sugarman, 2004). Better definitions are not likely to eliminate that variability.

According to Dr. Nelson, ethical barriers to the study of pediatric drugs fall into four categories:

- Clinicians are willing to prescribe drugs off label without sufficient pediatric data (adults, of course, are prescribed drugs off label as well). This willingness to use drugs without sufficient data results in delays in needed research.
- Sponsors, as expected, act in their financial self-interest. They often pursue pediatric clinical trials late in a drug's life cycle, after its true market value has been determined. Once they have decided to conduct a trial, cost considerations may trump considerations of study design quality.
- Academic institutions do not reward investigators for participat-

[1]This section is based on the presentation of Dr. Robert Nelson, Associate Professor of Anesthesiology and Critical Care, Children's Hospital of Philadelphia.

ing in clinical trials. Their goal is to have independent investigators with National Institutes of Health (NIH) R01 grants, not co-investigators in multi-institutional trials. A discordance exists between academic and industry goals in terms of data use, publication, and intellectual property. There is also a lack of academic interest in investigating old drugs.

- All levels of the clinical research enterprise lack transparency, which undermines the public trust. Factors contributing to this lack of transparency include the following:

  –Absence of justification for requested studies in FDA Written Requests

  –Potential wasted effort in the NIH Request for Proposals process for off-patent drugs (Dr. Nelson suggested that, in seeking a study to collect data on a drug, NIH should simply hire a third party to conduct the study, rather than soliciting proposals that require a great deal of grant writing.)

  –A closed IRB system. A transparent system would allow the public to be informed about the substance of the decisions made, not just the decision process. The public would also know of failures and delays by the industry in investigating or publishing information on adverse events

In closing, Dr. Nelson suggested that the ethical principles mentioned above pose barriers not to the responsible conduct of appropriately designed pediatric studies, but to studies that should not be conducted. The barriers that exist to appropriate studies may instead arise from a reluctance to alter existing practices and focus on the goal of finding efficient and effective ways to develop adequately studied drugs for the treatment of children.

In responding to Dr. Nelson's presentation, Dr. Alan Fleischman, a member of the audience from the New York Academy of Medicine, noted that several major reviews of Subpart D definitions have been performed in the past 5 years by the National Human Research Protections Advisory Committee, two Institute of Medicine (IOM) committees, and the Secretary's Advisory Committee on Human Research Protection. He raised the question of whether those reviews are adequate in light of clarifications soon to be published by the Office of Human Research Protections. Dr. Fleischman and Dr. Stephen Spielberg, a member of the audience from Dartmouth University, also raised the question of a child's ability to give informed consent, but the question was not answered by the panelists.

When asked whether a centralized IRB would address the issues he had raised, Dr. Nelson responded that this would be a potential solution if transparency were the result. He pointed to the facilitated IRB used by the National Cancer Institute (NCI): NCI sends the local IRB a package that describes the NCI IRB decision-making process and how the specific

issues within that protocol were analyzed. In his view, this approach provides the local IRB with sufficient information to decide whether the process and the determination make sense.

Ethical considerations will continue to be an important aspect of pediatric drug studies. Better definitions of risk categories, direct benefit, and other concepts would be helpful. Dr. Murphy suggested that oversight of trials needs to be an ongoing, active process, and that more transparency for all pediatric studies and resulting data is needed.

Economic Barriers[2]

According to Dr. Giacoia, economic factors are the major barriers to the development of better formulations for children. These barriers include relatively small market size and perceived high risk, as well as, for small companies, the cost of maintaining a pediatric sales force.

The relatively small market for pediatric drugs is economically unattractive for many large companies. U.S. pharmaceutical sales were $250 billion in 2005, and the annual sales growth rate is 5.4 percent. In contrast, U.S. pediatric pharmaceutical sales in 2005 were $37 billion, with an annual growth rate of 4 percent. The majority of the pediatric market is concentrated in a few therapeutic areas, such as anti-infective, central nervous system, allergy, and asthma drugs. The pediatric drug market is further segmented by the need for differing formulations and dosing for different age groups.

In addition, testing of drugs in pediatric populations is considered to be high risk, with little expected return on investment. When adverse events occur in a trial, sponsors face product liability risks, as well as the risk of having to add a warning to the product label. An example is the elevated risk of suicide in adolescents taking selective serotonin reuptake inhibitors (SSRIs), which was made public because the pediatric trials were conducted under the Best Pharmaceuticals for Children Act (BPCA).

Logistical and Technical Issues[3]

The infrastructure needed to effectively conduct pediatric drug studies is lacking, according to several of the workshop speakers. As noted

[2]This section is based on the presentation of Dr. George Giacoia, Project Director of the Pediatric Pharmacology Research Units Network, National Institute of Child Health and Human Development.

[3]This section is based on the presentation of Dr. Richard Gorman, Chair of the Section on Clinical Pharmacology and Therapeutics, American Academy of Pediatrics.

by Dr. Gorman, the number of pediatric pharmacologists is declining. Therapeutics is no longer, or rarely, taught in medical schools. In addition, too few physician scientists are able to conduct research that bridges the gap between basic science and clinical practice. Pediatric clinical research units are rare, and pediatric expertise on IRBs is limited, with the exception of children's hospitals.

Significant technical barriers to pediatric drug testing also exist. Dr. Gorman cited limited baseline information on frequency of disease and treatments of choice. According to Dr. Murphy, accepted endpoints and validated pediatric assessment tools are also lacking. In addition, she emphasized that defining the pediatric-specific adverse events associated with a drug is critical so that the pediatrician and the family know what events to look for and how to manage them. Without such knowledge, the common response when an event occurs is to stop use of the drug; however, it could be more appropriate to adjust the dosage or manage the effects.

During the discussion of Dr. Gorman's presentation, Dr. Robert Califf of the Duke University Medical Center and a member of the IOM Forum on Drug Discovery, Development, and Translation identified an issue that he believes is critical and needs to be discussed more openly: the pharmaceutical industry routinely seeks scientists outside of the United States to conduct studies because the nation's pediatric clinical research capability is not adequate for the purpose. In addition, as noted earlier, major academic institutions in the United States fail to reward pediatricians for conducting clinical research. Dr. Califf suggested that the IOM needs to help address these issues. Dr. Spielberg agreed, adding that the United States has the technologies in molecular biology, proteomics, and metabolomics to be able to conduct the needed studies. However, most institutions, including those with well-known pediatric hospitals, are not set up to perform the studies effectively and efficiently. Dr. William Evans, Director and CEO, St. Jude Children's Research Hospital, noted that one clear exception is childhood cancer, for which more than 70 percent of patients are treated in clinical trials, and Phase I and II drug studies are common.

Industry Perspective on Barriers to Pediatric Drug Development[4]

Ms. Jarrett and Mr. Hassall provided presentations on the barriers to pediatric drug development from the perspective of the industry, echo-

[4]This section is based on the presentations of Ms. Natasha Jarrett, Director of Regulatory Affairs, Hoffmann-LaRoche, and Mr. Thomas Hassall, Senior Director of Global Scientific, Medical, and Regulatory Affairs, Abbott Laboratories.

ing many of the points made by previous speakers. Ms. Jarrett noted a shift away from protecting pediatric patients against experimentation and toward protecting them through the generation of data from drug trials. She discussed the industry's ethical incentives to conduct research in pediatric populations, including the responsibility to share pharmaceutical knowledge with the community and to protect pediatric patients and further their treatment through provision of the data generated by industry trials. Current regulations, in particular those associated with the Pediatric Research Equity Act (PREA), have led the industry to think about conducting pediatric research much earlier in a drug's development, often at the very beginning.

Ms. Jarrett noted further that for every incentive, there are challenges in pediatric drug development. Trial designs for pediatric patients differ greatly from those for adult patients in the same disease area (see Box 3-1). Recruitment of subjects is also a difficulty for pediatric trials. Pediatric patients are recruited from different sites than adult patients, sites for which the networks and infrastructure necessary for recruitment are often not in place. The pediatric population is also smaller than the adult population, and sufficient numbers of subjects are frequently not available in one country. Sponsors must therefore go outside the United States or the European Union to recruit enough patients, particularly in the younger age groups. Doing so necessitates the involvement of more than one health authority (comparable to the FDA) and several ethics commit-

BOX 3-1 Differences Between Adult and Pediatric Trial Designs

- The nature of the disease can be different, requiring different endpoints.
- There are more restrictions on pediatric trials; for example, the volume of samples that can be taken requires more innovative statistical design.
- There are additional safety considerations, such as growth and development, in pediatric trials.
- "Pediatric" patients include neonates through adolescents, with very different considerations for each age group.
- The formulation of a drug needs to be different for younger and older patients.
- The expertise needed for pediatric trials often is not available in house, so external experts need to be consulted.

SOURCE: Jarrett, 2006.

tees. Regulatory agreements on protocols or Written Requests can require many rounds of feedback and sometimes years to achieve, particularly if more than one health authority is involved.

Ms. Jarrett suggested that technical and preclinical difficulties also exist. For example, as discussed earlier, adult formulations are not always suitable for pediatric patients. Reformulation work can take years and involve special considerations, such as palatability. Sometimes reformulation is not possible or feasible, but years can be required to obtain an agreement that due diligence has been exercised.

Mr. Hassall observed that the incentives for pediatric trials have not changed since the inception of pediatric exclusivity through the FDA Modernization Act (FDAMA) in 1997, but expectations have grown: to obtain the 6-month exclusivity, more effort is expected of a drug's sponsor. With BPCA, the emphasis has shifted from developing information on how to use currently available drugs to developing an entirely new product line for pediatric populations, but with no additional incentives. In addition, the Prescription Drug User Fee Act (PDUFA) used to exempt pediatric applications from user fees; however, this is no longer the case. Therefore, companies seeking to develop a pediatric formulation, submit an application to the FDA, and get a drug on the market now face a cost of three-quarters of a million dollars for the drug to be reviewed. Mr. Hassall concluded that "the challenge is to try to strike a balance between expectations and incentives for the next decade."

Ms. Jeanne Ireland, a member of the audience from the Elizabeth Glaser Pediatric AIDS Foundation, asked Mr. Hassall about his view of proposals to tier the size of the incentive according to the cost of the study or the profit or sales of the product. Mr. Hassall responded that he does not believe this to be the best solution. FDAMA presented an elegant solution because it limited the scope of the behavior expected of the industry, focusing on the goal of generating data and information for labeling.

FORMULATIONS[5]

According to Dr. Giacoia, a significant number of drug formulations are not suitable for children. Each type of formulation poses difficulties, depending on the age of the child. Younger children, for example, may be unable to swallow pills, may spit out chewable tablets, and may dislike effervescent tablets. As a result, physicians frequently manipulate existing formulations for use in children. These extemporaneous formulations may be unsafe, as quality control is often lacking; moreover, the process may include the compounding of drugs, which carries additional risks. For most

[5]This section is based on the presentation of Dr. Giacoia.

drugs, however, suitable formulations and administration pathways are possible.

Dosing instruments may be as important as the formulation itself. Many medications for children are in the form of oral liquid preparations, which are often dispensed from droppers and teaspoons. Because tableware teaspoons can vary in capacity from 4 to 7 mL, medication errors can occur unless a measuring instrument is provided with the medication. In addition, appropriate testing of drug taste and palatability—important to adherence among pediatric populations—is lacking. The science of blocking bitter taste, for example, is in its infancy. Alternatives to oral liquid formulations are needed. One alternative dosing instrument is a patch, but it is difficult to keep a patch on a child unless it is placed on the back, and an occlusive dressing may be needed to keep it in place. In addition, there are major gaps in knowledge regarding different drug delivery systems.

The recently launched Pediatric Formulations Initiative has several aims:

- To identify on- and off-patent drugs for which no suitable formulations are available
- To determine scientific and technical barriers to the development of pediatric formulations
- To summarize current knowledge on drug palatability, taste masking, bitterness reduction, and pediatric taste studies, and to identify gaps in knowledge in these areas
- To determine current knowledge of the toxicity of flavorings, dyes, sweeteners, and preservatives
- To identify current practices for dispensing drugs without appropriate pediatric formulations and to determine the suitability of different methods for oral administration
- To identify regulatory issues that affect the development and approval of pediatric formulations
- To create a forum for information exchange

To carry out this initiative, four working groups composed of representatives from industry, academia, the FDA, and NIH were formed. The first planning session was held in December 2005.

For a pilot study on extemporaneous formulations, the initiative is seeking the participation of about 30 children's hospitals in the United States and Canada. A detailed survey will include both inpatient and outpatient children, and will solicit financial information, determine the extent of use of and deviation from published formulations, and identify those drugs for which formulation stability data are needed.

DOSING, BIOAVAILABILITY, AND DRUG RESPONSE[6]

When pediatric labeling information is lacking, pediatricians often refer to the available scientific literature to estimate dosing for children. If such studies exist, they are frequently based on very small, selected populations. Dr. Ward gave a neonatologist's perspective on treating newborns, whom he views as the most susceptible pediatric patients. He provided several examples of how pharmacokinetics and organ function (such as that of the heart and the kidneys) vary in important ways among a 23-week premature infant, a 30-week premature infant, and a 40-week full-term infant. He also cited studies that have revealed ethnic variations in the distribution of certain enzymes that cause faster or slower metabolism of drugs. Moving from dose guessing to informed prescribing will require additional studies of the pharmacokinetics, safety, and efficacy of new drugs and older, off-patent drugs. Those studies will need to be coupled with the study of developmental variations relevant to dosing, such as changes in drug clearance, during the first few months after birth and beyond.

In responding to Dr. Ward's presentation, Dr. Snodgrass described some shortcomings in the existing framework for pediatric drug use. Although the current system offers a good mechanism for testing on-patent drugs (see the discussion of this issue in Chapter 2), it falls short for older, off-patent drugs. With a common drug such as morphine, little information is available on optimal use and basic pharmacokinetics in different age groups. Dr. Snodgrass also expressed concern that pediatricians lack a good evidence-based reference for making prescription decisions. For example, there is disagreement on whether dosing should be based on weight or surface area. Dr. Snodgrass further suggested that dissemination of information to physicians could be improved so they can make the best choices in prescribing medications for individual patients. Finally, Dr. Snodgrass and others seconded Dr. Giacoia's emphasis on the importance of the taste and formulation of a drug to adherence in pediatric patients—more so than is the case with adults.

[6]This section is based on the presentation of Dr. Robert Ward, Director, Pediatric Pharmacology Program, University of Utah.

4

Models for Enhancing Pediatric Drug Development

The need to identify other models for enhancing drug discovery and development for pediatric populations was addressed by several speakers. Potential models that were presented and discussed included vaccine development in the United States, an incentive-based model based on the European Union's (EU's) new regulatory approach, and an academic health center initiative exemplified by the model developed by St. Jude Children's Research Hospital.

VACCINE DEVELOPMENT IN THE UNITED STATES[1]

Vaccine development in the United States can offer lessons for pediatric drug development. Both vaccines and drugs are covered by the Pediatric Research Equity Act (PREA), and requirements for safety and efficacy are similar. In addition, both vaccines and drugs are often tested initially in adults. While the similarities stop there, according to Dr. Orenstein, two of the systems in place for vaccines—public information fact sheets and the no-fault compensation system—may be helpful models for pediatric drugs.

In 1986, vaccines were available to prevent 8 diseases in children; vaccines today prevent 16 diseases. However, vaccine development is difficult and costly; only a handful of large pharmaceutical companies

[1]This section is based on the presentation of Dr. Walter Orenstein, Professor of Medicine and Pediatrics, Emory University.

dominate the vaccine market. Exclusivity is not an incentive because there are no competitors waiting to produce generic versions of vaccines.

Several incentives do exist for vaccine development, some by virtue of what vaccines do and how they are distributed, and some that were put in place specifically to spur development. Vaccine makers are often guaranteed a large market because of universal vaccination policies that reflect standards of care set by recommending bodies. Vaccines are fundamental to pediatric practice and are a regular component of well-clinic visits. Moreover, vaccination often offers protection to the community as well as to individuals; therefore, many vaccines are eventually mandated through school and/or day care laws.

Because vaccines are mandated to provide a community benefit, Congress established the National Vaccine Injury Compensation Program as Title XXI of the Public Health Service Act of 1987. The program offers a no-fault compensation system for patients (or their families) who suffer serious adverse reactions from required childhood vaccines. The aim is to help stabilize the supply and price of vaccines by removing most of the liability burden from manufacturers for immunization-related injuries. The program is funded by an excise tax of $0.75 on every dose of covered vaccine that is purchased.

Also in place is the Vaccine Adverse Event Reporting System (VAERS), a national vaccine safety surveillance program that collects information about adverse events occurring after the administration of U.S.-licensed vaccines. Reports are made by vaccine manufacturers, health care providers, state immunization programs, vaccine recipients, and other sources. VAERS is a passive system (meaning that reporting is generally voluntary), though certain adverse events are required to be reported by law. Two-page public information fact sheets on each vaccine describing benefits and risks, issued by the government and written for the lay public, also stimulate reporting by consumers. In addition, the Vaccine Safety Data Link (VSDL) was established to monitor immunization safety and address gaps in knowledge about rare and serious side effects associated with immunizations. It monitors rates of adverse events from eight managed care organizations that cover roughly 2 percent of the population. VAERS works by identifying signals that indicate there may be a problem, while VSDL is better for assessing causality.

Dr. Orenstein suggested that two components of vaccine development might transfer well to pediatric drug development: the fact sheets used for vaccines would likely be helpful for pediatric drugs as well, and a no-fault compensation system could remove a barrier to the industry's testing and distribution of products among pediatric populations. Dr. Orenstein also suggested development of a document similar to the *Red Book*, a pediatric infectious disease reference

produced by the American Academy of Pediatrics' (AAP's) Committee on Infectious Diseases.

In the discussion following Dr. Orenstein's presentation, Dr. Ward described an AAP collaboration with the Royal College of Pediatrics in the United Kingdom to develop a drug handbook for pediatrics that would include off-label prescribing information based on expert opinion. The key challenge, he noted, is correlating adverse events with exposure to medications.

Dr. Murphy emphasized the importance of making the public aware of the depth of the problem; without significant changes, she suggested, we are essentially experimenting on children in an uncontrolled manner. The Adverse Event Reporting System, the Food and Drug Administraton's postmarket safety surveillance program for all approved drugs and therapeutic biologic products, is similar to VAERS, but Dr. Murphy noted that there is tremendous underreporting. She indicated that she would prefer to see an active surveillance system.

THE EUROPEAN UNION'S NEW REGULATORY APPROACH[2]

Dr. Weyersberg described a new EU regulation on pediatric drug development. The regulation, which entered into force on January 26, 2007, is applicable and obligatory for all 25 EU member states. Its goals include improving the health of children by fostering high-quality, ethical research on pediatric medicines; increasing the availability of medicines authorized for children; and expanding the information base on the use of medicines in pediatric populations. The objective is to achieve these goals without conducting unnecessary studies in children and without delaying authorization for adults.

The regulation has five major components:

- The formation of a new Pediatric Committee working at the European Agency for the Evaluation of Medicinal Products (EMEA) in London
- Incentives for patent-protected medicinal products
- Incentives for off-patent medicinal projects
- The Pediatric Investigation Plan (PIP)—a document describing proposed studies of the drug in pediatric populations, which must be approved by the Pediatric Committee and must be complied with if the associated incentives are to be received

[2]This section is based on the presentation of Dr. Annic Weyersberg, National Expert Paediatrics, European Agency for the Evaluation of Medicinal Products. The information provided in this section is based on information available in 2006, and may have been subject to changes in the course of the implementation process. For more detailed and up-to-date information on the EU Pediatric Regulation, refer to the EMEA website: www.emea.europa.edu.

- Several additional measures that also support pediatric drug development

The Pediatric Committee

The Pediatric Committee will consist of one representative and one alternate from each EU member state, five of whom will also be members of the Committee on Human Medicinal Products (the EU committee that recommends the granting of marketing authorization for new medicinal products submitted through the centralized procedure), as well as six members and alternates to represent health professionals and patient associations. The committee will include experts in pediatric research, pharmacology, pharmacy ethics, clinical science, and other areas. It will meet three days a month to assess and make opinions on PIP applications, including deferrals and requests for waivers.

Incentives

Incentives will vary according to whether a product is patent-protected, off-patent, or an orphan drug. For patent-protected products, submission of an application for marketing authorization or any application for a variation will incur a new obligation to provide study results in accordance with an agreed-upon PIP. The reward will be a 6-month extension of the patent protection (supplementary protection certificate).

Older, off-patent products will be able to receive a new form of marketing authorization called a Pediatric Use Marketing Authorization (PUMA). A PUMA will be granted on the basis of studies conducted in children that lead to an authorization for use in children, including a specific pediatric formulation, also according to an agreed-upon PIP. The reward for submitting pediatric study results will be a 10-year period of data protection. The applicant will be able to use the existing brand name for the product for adults and place a symbol on the label to show that there is a pediatric indication as well. In contrast with patent-protected products, however, applying for the new authorization and subsequent reward will be optional for off-patent products.

An incentive for orphan drugs will also exist. Dr. Weyersberg said this is important because 15 to 20 percent of rare diseases affect only children, while 55 percent affect both adults and children. Upon submission of study results according to an agreed-upon PIP, the reward will be 2 years of extra market exclusivity in addition to the existing 10 years. Thus, a sponsor of an orphan product will have 12 years of market exclusivity if it has conducted studies in children.

In each case, the rewards will be granted even if the results of the studies conducted fail to lead to authorization of a pediatric indication. The intent is to reward the effort made to collect pediatric data.

Pediatric Investigation Plans

The PIP will be a detailed document describing proposed studies for the preclinical and clinical development of a drug for use in pediatric populations. It will include the schedule for the studies and the means to be used to demonstrate quality, safety, and efficacy. It will also describe how the drug's formulation will be adapted for children, with consideration of different pediatric populations. Each PIP will be assessed and must be approved by the Pediatric Committee, and will be binding if the sponsor is to receive the incentives described above. The committee will have a maximum of 120 days to review the PIP. There will be an option to amend an agreed PIP, but the Pediatric Committee must approve each amendment. The PIP will also include justification for any waivers or deferrals—for example, if there is no significant therapeutic benefit over existing treatments for children or for a particular pediatric population, or if it is more appropriate to initiate studies in children after sufficient data for adults are available.

Additional Measures

All applicants will be eligible to receive free scientific advice from the EMEA on the design and conduct of pediatric studies and on pharmacovigilance measures for the postauthorization period. Each EU member state will have to collect all available data on existing uses of all medicinal products in children. They will have 2 years to collect these data, which will be assessed by the Pediatric Committee so that an inventory of therapeutic needs can be developed. A European Research Network will be established at the EMEA to link existing networks, investigators, and centers with expertise on studies in pediatric populations.

The regulation is expected to increase transparency because, unlike results of studies in adults, results of all pediatric studies, completed and ongoing, will be publicly available. Community funding will be available for studies of off-patent medicines. Funding will be determined on the basis of the needs identified in the inventory mentioned above.

If a pharmaceutical company benefits from the rewards described above but then wishes to withdraw the product from the market, it will have to transfer the marketing authorization to an interested third party or provide access to the data on the product.

Obligations and Postauthorization Requirements

Rewards will come with two major obligations. First, study results must be included in the summary of product characteristics and, if appropriate, in the product's package leaflet. Second, the product must be authorized in every EU member state so that all children in the EU may benefit. There are also postauthorization requirements, including the stipulation that applicants must place the product on the market within 2 years after receiving a reward. In addition, the Pediatric Committee can ask the applicant to propose measures for ensuring long-term follow-up on safety, a risk management system or risk minimization plans, and specific postauthorization studies.

THE ST. JUDE'S MODEL FOR PEDIATRIC ONCOLOGY DRUGS[3]

St. Jude Children's Research Hospital in Memphis has assumed the challenge of bringing new molecularly targeted therapies to bear on children's cancer research. Until now, none of the research focused on personalizing cancer treatments by directly targeting the molecular changes that occur within an individual has focused on childhood cancers. Imatinib (Gleevec, for chronic myeloid leukemia), trastuzumab (Herceptin, for breast cancer), and other drugs in the development pipeline are all intended for the treatment of adult cancers. However, molecular abnormalities in pediatric cancers are distinct from those in adult cancers. As with pediatric medications generally, market forces work against the development of pediatric cancer drugs. Each year 9,000 pediatric cancers are diagnosed in the United States, compared with a much larger number of adult cancers (e.g., 200,000 new breast cancer cases, 190,000 prostate cancer cases, and 160,000 lung cancer cases). These 9,000 pediatric cases comprise 50 to 100 different types of cancer. Despite impressive progress made in the cure rates for childhood cancers by using adult anticancer agents, cancer remains the leading cause of death by disease in U.S. children over 1 year of age. Furthermore, less toxic therapy is needed to ensure a better quality of life for pediatric cancer survivors.

The St. Jude's model is an effort to follow through on the 2005 Institute of Medicine report *Making Better Drugs for Children with Cancer* (IOM, 2005). That report called for public–private partnerships to lead the discovery and development of pediatric cancer drugs so that children can benefit from the new wave of science and molecularly targeted medicine for cancer.

[3]This section is based on the presentation of Dr. Evans.

Dr. Evans and others convened a group of doctors and scientists to create a scientific plan that would clearly outline what needed to be done to develop new drugs for pediatric cancers. The effort involved partnerships with academia, large and small pharmaceutical companies, government health agencies, and philanthropic foundations.

St. Jude Children's Research Hospital has focused on filling the gap in the discovery of pediatric cancer drugs by building a Good Manufacturing Practices (GMP) facility, and launching a Chemical Biology and Therapeutics initiative. There is interest in leveraging these efforts through the National Cancer Institute's (NCI's) Pediatric Cancer Drug Discovery Consortium under an expanded public–private–government initiative. The GMP facility is producing gene therapy vectors, vaccines, and monoclonal antibodies. The Chemical Biology and Therapeutics initiative will involve putting viable targets in pediatric tumors from the research laboratories of St. Jude's and others through high-throughput screens of very large libraries of small molecules—currently more than 1 million compounds. This is similar to the type of drug screening a pharmaceutical company might conduct, although St. Jude's has objectives other than simply developing new drugs. The goals are to identify small molecules that are inhibitors of specific targets in pediatric cancers and could be used to explore the pathways involved in pediatric cancers, identify candidate small molecules for preclinical testing, and network with others to improve capacity and ultimately advance these agents to the level of the pediatric clinic. Finally, NCI is funding the Pediatric Cancer Drug Discovery Consortium to screen adult cancer drug candidates in animal models with pediatric tumors.

In response to Dr. Evans' presentation, Dr. Nelson raised concerns about relying on independent, well-funded pediatric institutions to compensate for the deficits in funding for traditional academic research. Dr. Evans replied that all involved need to do what they can, and that he is concerned about the flat funding for the National Institutes of Health. To address the funding issue, he plans to rely more on team science, looking to academic partners and others for what they do well.

Dr. Susan Weiner, a member of the audience from the Children's Cause for Cancer Advocacy, asked whether St. Jude's expects to file a New Drug Application if an entity is found that is effective in only a small group of children. Dr. Evans replied in the affirmative and noted that St. Jude's has acquired various libraries of compounds through different arrangements. Some have been purchased outright; others involve the right to first refusal if a lead compound or potential therapeutic is found. Dr. Evans warned that, with molecular characterization of tumors, more and more drugs will be found to be useful in smaller subsets of patients. A new business model needs to be devised for the development of these drugs with small potential markets, a need that is growing for adult diseases as well.

5

Challenges and Opportunities for the Future

Despite progress made in the development and study of drugs for use in pediatric populations, many such drugs have not been tested substantially in children. Accordingly, workshop participants discussed ways to achieve further progress. The discussion addressed both systemic solutions and potential means of eliminating the economic barriers reviewed in Chapter 3.

SYSTEMIC SOLUTIONS

Speaking as a pediatrician, Dr. Murphy offered several suggestions for improving the system for pediatric drug research:

- More transparency in research
- Continued development of pediatric endpoints and assessment tools
- Real-time inspections of pediatric trials
- Continued development of juvenile animal models
- Better approaches to assessing the long-term safety of drugs
- Active surveillance systems focused on pediatric populations
- More studies in neonates and premature infants

Dr. Murphy asserted that pediatric drug development must become more global because pediatric populations are smaller than the adult

population, children are protected from participation in studies, and there is little commercial motivation to test drugs in children.

Surveillance

Dr. Murphy stressed that, because pediatric drugs are studied in a very limited population in a very defined way, a great deal of the safety information on these products emerges only after they have been marketed. Her call for the collection of data on long-term outcomes, with better postmarket safety surveillance, was echoed throughout the meeting. Dr. Snodgrass asserted that postmarket surveillance must be more extensive and thorough than is the case today. It needs to encompass adverse events as well as other outcomes and to quantify long-term benefit. Dr. Fleischman suggested that the only way to make postmarket surveillance feasible is to support the development of uniform electronic medical records with appropriate privacy protections.

Regulation

Dr. Murphy also suggested combining incentives and requirements for conducting research in pediatric populations into one process, as the Europeans have done. In the United States, the two are handled separately in the legislative process and within the U.S. Food and Drug Administration (FDA). Summaries of research should be available to the public for studies that fall under both the Best Pharmaceuticals for Children Act (BPCA) and the Pediatric Research Equity Act (PREA). How much information would be provided and in what format would have to be determined. Dr. Nelson suggested that Written Requests should be made public, as knowing what the FDA is asking a sponsor to do is helpful in evaluating what the sponsor has actually done.

Ms. Ireland seconded the call for greater transparency, adding that there is also a need for better coordination of studies done under PREA and BPCA. She suggested that there is no reason why the Pediatric Advisory Committee reviews adverse events for BPCA and not for PREA studies. In addition, Ms. Ireland favors looking beyond pediatric-specific laws to the broader movement in Congress to address drug safety issues. The Senate Health, Education, Labor, and Pensions (HELP) Committee is exploring the idea of broadening the authority of the FDA to require postmarket studies and is considering the development of a clinical trials database.

According to Dr. Ward, the PREA requirement that pediatric studies be requested only for those indications applied for in adults is too limiting. Multiple examples can be cited in which new therapeutic uses have

emerged during a product's lifespan. An example is sildenafil (Viagra), which is now used for pulmonary hypertension in premature infants but was developed for erectile dysfunction.

Ms. Ireland cautioned that reauthorization of BPCA will require Congress to address new cost issues because of the recent changes resulting from the Medicare prescription drug benefit. The benefit is likely to increase costs to the government, so cost–benefit considerations will be central to the reauthorization debate. Dr. Snodgrass responded that the cost of not conducting pediatric studies should also be examined.

Training and Research

Several participants expressed the need for more physician training. Dr. Spielberg called for better training in therapeutics in medical school because many of today's physicians do not fully understand how to use drugs wisely. Physicians must not only be able to understand drug labels, but also be thoughtful in challenging the labels on the basis of good pharmacological principles. Dr. Ward added that the majority of medical schools fail to recognize therapeutics as a discipline to be taught to students. As a result, the importance of clinical drug studies is not fully recognized.

Dr. Patricia Horsham, a member of the audience from the College of Physicians and Surgeons in Canada, noted that drug companies are approaching pediatricians in private practice to recruit patients for clinical trials so they will not have to deal with the stringent rules for academic research. Pointing to the Pediatric Research in Office Settings (PROS) Network of the American Academy of Pediatrics, Dr. Spielberg suggested that office-based pediatricians are an opportunity. This approach finds favor among pediatric practitioners because they believe they are participating in the development of new knowledge. Dr. Spielberg encouraged the development of more networks of primary care pediatricians to participate in such efforts under the proper auspices and ethics.

Finally, Ms. Ireland agreed with others who stated that off-patent studies are not optimally conducted through the Foundation for the National Institutes of Health (FNIH), which relies on charitable contributions for the necessary support. Dr. Mathis acknowledged that the National Institutes of Health (NIH) also has had difficulty in securing funding for off-patent studies. Additional federal funding for these studies is needed.

ELIMINATION OF ECONOMIC BARRIERS

Dr. Giacoia outlined several possible solutions to the economic barriers to pediatric drug studies. The following solutions were devised by

the Economics and Partnerships Working Group of the Pediatric Formulations Initiative:

- Development of global standards for oral liquid preparations, and expansion of the market for these preparations by combining incentives for pediatric and geriatric populations
- A reduction in cost, risk, and time-to-market
- Use of "existing" formulations (some pharmaceutical companies produce formulations that do not enter commercial use, so perhaps they could donate these formulations to not-for-profit organizations)
- Importation of approved pediatric drugs (several products are approved in Europe and other countries but are not available in the United States; legal, regulatory, and legislative issues would need to be addressed)
- Additional incentives (limited exclusivity), funding, and tax breaks
- Incentives for priority extemporaneously formulated drugs
- Incentives for pediatric formulations of generic drugs (similar to the 12 years of data exclusivity granted by the European union)
- Public–private partnerships for orphan drugs

CONCLUDING THOUGHTS

Several themes emerged from the workshop as participants discussed how to move pediatric drug development forward to spur more research and improved safety.

The current regulations, both of which sunset in 2007, have had an important positive effect on pediatric drug development. Both industry and FDA participants agreed that PREA has led drug developers to think about pediatric applications when they begin developing a drug for an adult condition that exists in children as well. Furthermore, the incentive of expanded market exclusivity under BPCA has improved the labeling on more than 100 medications for children.

Many participants agreed that incentives work, but perhaps more are needed. Additional incentives worth exploring are limited liability, incentives to work on formulation and taste issues to improve pediatric patient adherence, and debt forgiveness for students entering academic careers in pediatrics and clinical investigation. Dr. Califf, remarking on the need for transparency and the difficulties of finding information on the FDA website, also suggested an incentive to display publicly how a study was conducted and what its results were, as well as how its results should be interpreted.

Dr. Spielberg said that the FDA will be dealing with greater uncer-

tainty and more risk with the new compounds now in the pipeline, in terms of both the costs of studies and market size. Because none of these factors bode well for encouraging drug makers to test their products in children, Dr. Murphy stressed that incentives may become more important than ever.

An additional challenge is funding for off-patent studies. Dr. Mathis and others suggested that relying solely on FNIH for funding for these studies is unrealistic. Dr. Nelson also argued that the process used by NIH to get contracts for studies of these drugs, as well as for on-patent drugs that a sponsor chooses not to study, is cumbersome and unnecessarily lacking in transparency.

A number of participants, including Dr. Gorman and Ms. Jarrett, agreed that the infrastructure needed to conduct multisite pediatric studies is lacking. Enhancing this infrastructure would require not only the additional training in therapeutics discussed above, but also increased funding for practice-based research networks. In addition to better training, increasing the numbers of trained pediatric clinical investigators is also important; the debt forgiveness for students incentive mentioned earlier could be helpful in this regard.

Pediatric-specific adverse events must also be defined so that pediatricians and parents will know what to look for and how to manage events that occur. Dr. Murphy and Dr. Snodgrass advocated for a more active surveillance system to identify adverse events, especially after a pediatric indication has been approved for marketing. They also stressed the importance of better communication to prescribers and consumers so they will know not only how to deal with adverse events, but also how to use the medications properly.

Finally, lessons can be learned from the European Union's recent regulations, which represent a coordinated effort to improve the study of on-patent, off-patent, and orphan drugs. The compensation fund and information sheets that are integral to vaccine drug development can also serve as models for pediatric drug development.

References

Budetti, P. 2003. Ensuring safe and effective medications for children. *Journal of the American Medical Association* 290:950–951.

FDA (Food and Drug Administration). 2006. Drug research in children. *FDA Consumer Magazine*. http://www.pueblo.gsa.gov/cic_text/health/testtube/children.htm (accessed November 28, 2006).

Floren, L. C., A. Wiznia, S. Hayashi, A. Jayewardene, K. Stanley, G. Johnson, S. Nachman, P. Krogstad, F. T. Aweeka, and Pediatric AIDS Clinical Trials Group 377 Protocol Team. 2003. Nelfinavir pharmacokinetics in stable human immunodeficiency virus-positive children: Pediatric AIDS Clinical Trials Group Protocol 377. *Pediatrics* 112:e220–e227.

ICH (International Conference on Harmonization). 2000. ICH harmonised tripartite guideline: Clinical investigation of medicinal products in the pediatric population E11. Current Step 4 version dated 20 July 2000. http://www.ich.org/LOB/media/MEDIA487.pdf (accessed January 22, 2007).

IOM (Institute of Medicine). 2005. *Making better drugs for children with cancer*. Washington, DC: The National Academies Press.

Jarrett, N. 2006. *Incentives and disincentives for pediatric drug development*. Speaker presentation at the Institute of Medicine Workshop on Addressing the Barriers to Pediatric Drug Development, June 13, 2006, Washington, DC.

Kearns, G. L., S. M. Abdel-Rahman, S. W. Alander, D. L. Blowey, J. S. Leeder, and R. E. Kauffman. 2003. Developmental pharmacology—drug disposition, action, and therapy in infants and children. *New England Journal of Medicine* 349:1157–1167.

Mathis, L. 2006. *Growth and development of pediatric drug development at the FDA*. Speaker presentation at the Institute of Medicine Workshop on Addressing the Barriers to Pediatric Drug Development, June 13, 2006, Washington, DC.

McKinney, R. E. 2003. Congress, the FDA, and the fair development of new medications for children. *Pediatrics* 112:669–670.

Roberts, R., W. Rodriguez, D. Murphy, and T. Crescenzi. 2003. Pediatric drug labeling: Improving the safety and efficacy of pediatric therapies. *Journal of the American Medical Association* 290(7):905–911.

Rodriguez, W. 2006. *What we have learned from the study of drugs under the pediatric initiatives*. Speaker presentation at the Institute of Medicine Workshop on Addressing the Barriers to Pediatric Drug Development, June 13, 2006, Washington, DC.

Sugarman, J. 2004. Determining the appropriateness of including children in clinical research: How thick is the ice? *Journal of the American Medical Association* 291:494–496.

Appendix A

Workshop Agenda

Forum on Drug Discovery, Development, and Translation
Addressing the Barriers to Pediatric Drug Development

June 13, 2006
8:00 am–4:30 pm
The National Academies

7:30 am Breakfast

8:00 am Opening Remarks by Discussion Moderator

Michael Katz, MD
March of Dimes Birth Defects Foundation

Current Development Procedures and Impact on Clinical Practice

8:10 am Richard Gorman, MD
American Academy of Pediatrics

8:25 am Wayne Snodgrass, MD, PhD
American Academy of Pediatrics Committee on Drugs

8:40 am Discussion

Regulatory Perspective

9:10 am *Historical and Regulatory Background*
Lisa Mathis, MD
U.S. Food and Drug Administration

9:25 am *Relabeling of Existing Drugs*
William Rodriguez, PhD, MD
U.S. Food and Drug Administration

9:40 am *Lessons Learned and Future Directions*
Dianne Murphy, MD
U.S. Food and Drug Administration

9:55 am Discussion

10:25 am Break

Incentives and Disincentives for Pediatric Drug Development

10:40 am *Ethical Issues Concerning Testing of New Drugs in Children*
Robert Nelson, MD, PhD
Children's Hospital of Philadelphia

10:55 am Natasha Jarrett
Hoffmann-LaRoche

11:10 am Thomas Hassall, RPh, MS
Abbott Laboratories

11:25 am Discussion

12:00 pm Lunch

Dose Finding and Bioavailability Guessing

1:00 pm Robert Ward, MD
University of Utah

1:15 pm *Best Pharmaceuticals for Children Act: Pediatric Formulation Issues*
George Giacoia, MD
National Institute of Child Health and Human Development, National Institutes of Health

1:30 pm Discussion

Could Vaccines Be a Possible Model for Pediatric Drug Development?

2:00 pm Walter Orenstein, MD
Vaccine Adverse Event Reporting System

2:15 pm Discussion

2:45 pm Break

Current Models and Alternative Approaches

3:00 pm *European Union Legislation*
Annic Weyersberg, MD
European Agency for the Evaluation of Medicinal Products

3:15 pm *St. Jude's Approach to Addressing the Institute of Medicine Report:* Making Better Drugs for Children with Cancer
William Evans, PharmD
St. Jude Children's Research Hospital

3:30 pm Discussion

Identification of Actions

4:00 pm Conclusions and Next Steps for the Institute of Medicine Drug Forum

4:30 pm Adjourn

Appendix B

Speaker Biographies

William E. Evans, PharmD, is Director and Chief Executive Officer of St. Jude Children's Research Hospital, and First Tennessee Bank Professor at the University of Tennessee Colleges of Medicine and Pharmacy. For the past 30 years, his research at St. Jude has focused on the pharmacogenomics of anticancer agents in children, for which he has received three consecutive National Institutes of Health (NIH) MERIT Awards from the National Cancer Institute. The major disease focus of his pharmacogenomics research has been on acute lymphoblastic leukemia in children. Dr. Evans has authored more than 300 articles and book chapters, has been the editor of several textbooks and scientific journals, and has received several national awards for his research. He was elected to the Institute of Medicine (IOM) in 2002.

George P. Giacoia, MD, is the Program Director of the National Institute of Child Health and Development (NICHD) Pediatric Pharmacology Research Network and the coordinator and planner of the NICHD Pediatric Formulation Initiative. Dr. Giacoia is a neonatologist whose research interest has been in the area of neonatal pharmacology.

Richard L. Gorman, MD, is a partner in the private practice of pediatrics. In prior years, he ran a pediatric emergency department and an ambulatory center and was the Medical Director of the Maryland Poison Center. A graduate of Catholic University, he received his MD from Downstate Medical School in Brooklyn, NY. His pediatric residency was at Children's

National Medical Center in Washington, DC. A general pediatric academic development fellowship at Johns Hopkins followed. He has been active in the American Academy of Pediatrics (AAP), serving on the Task Force on Terrorism, the Committee on Drugs, and the Section of Clinical Pharmacology and Therapeutics. Dr. Gorman is currently chair of that section. He has worked with AAP to ensure that drugs are both tested and labeled for the pediatric patient.

Thomas Hassall, RPh, MS, holds a bachelor of science degree in pharmacy from the University of Iowa and a master's degree in hospital pharmacy administration from the University of Minnesota. He served as a Commissioned Officer in the U.S. Public Health Service for 26 years, including 16 years at the Food and Drug Administration (FDA). Mr. Hassall's FDA experience includes regulatory positions in the Division of Cardio Renal Drug Products, the Division of Gastrointestinal and Coagulation Drug Products, the Division of Over the Counter Drug Products, the Office of the Center Director, and the Office of Drug Evaluation IV (ODE IV). While in ODE IV he worked on the implementation of the pediatric exclusivity provisions of the Food and Drug Administration Modernization Act and promulgation of the "pediatric rule." Mr. Hassall has 6 years of regulatory policy experience in the pharmaceutical industry, where he has continued his interest in pediatric drug development. He currently holds the position of Senior Director in Global Scientific, Medical, and Regulatory Affairs at Abbott.

Natasha D. Jarrett graduated from Oxford Brookes University with an honors degree in biology and has worked in regulatory affairs since 1997. Ms. Jarrett started her regulatory career at GlaxoWellcome, UK and subsequently moved to Hoffmann-La Roche in Hertfordshire, UK, where she worked on a range of local marketing and development projects. For the past 4 years, Ms. Jarrett has been working at Hoffmann-La Roche in the United States, with U.S. and global responsibility for a range of virology and dyslipidemia development projects. Ms. Jarrett is also the regulatory representative for U.S. pediatric strategy and development. She is currently Director, Regulatory Affairs at Hoffmann-La Roche, Nutley, NJ.

Michael Katz, MD, is Senior Vice President for Research and Global Programs, March of Dimes Birth Defects Foundation, Reuben S. Carpentier Professor, Emeritus of Pediatrics and Professor, Emeritus of Public Health at Columbia University. He is also consultant, emeritus to the New York–Presbyterian Hospital. He received an AB degree from the University of Pennsylvania, an MD degree from State University of New York, Downstate Medical Center, and an MS degree in tropical medicine

from Columbia University. He served an internship at the University of California Hospital, Los Angeles, and a residency at Babies Hospital in New York. He was an Assistant Professor of Pediatrics at the University of Pennsylvania and an associate member of the Wistar Institute of Anatomy and Biology in Philadelphia prior to his appointment as Professor of Public Health and Head of the Division of Tropical Medicine in the School of Public Health at Columbia University in 1970. In 1972, he became Professor of Pediatrics and Director of the Division of Infectious Diseases at Babies Hospital. From 1977 to 1992, he was the Reuben S. Carpentier Professor and Chairman of the Department of Pediatrics at Columbia University's College of Physicians and Surgeons and Director of Pediatric Service at Presbyterian Hospital (Babies Hospital) in New York. He has been in his current position since 1992. Dr. Katz is an internationally recognized expert in parasitic diseases, the relationship between malnutrition and infection, and viral pathogenesis. He is the author of numerous publications and has received a number of awards and honors, including the Senior U.S. Scientist Award of the Alexander von Humboldt Foundation in Germany and a Distinguished Service Award of the College of Physicians & Surgeons of Columbia University. He has served on advisory committees and as a consultant to the World Health Organization, UNICEF, USAID, and the IOM for his expertise in virology and in tropical diseases. Dr. Katz is a fellow of the American Society for the Advancement of Science, a fellow of the Infectious Diseases Society of America, and a member of the IOM.

Lisa Lee Mathis, MD, is a board-certified pediatrician in the U.S. Public Health Service with special interest and experience in counterterrorism and medical care of refugees and displaced persons. Dr. Mathis attended medical school at the Uniformed Services University of the Health Sciences and then did a residency in pediatrics at the University of California, Davis. After that, she practiced general pediatrics in inner cities, and currently practices at the National Naval Medical Center in Bethesda, MD. Dr. Mathis is also an Associate Professor of Pediatrics at the Uniformed Services University, where she teaches first- and second-year medical students in the classroom and third- and fourth-year medical students in the pediatric clinic.

Mary Dianne Murphy, MD, is the Director of the Office of Pediatric Therapeutics in the FDA's Office of the Commissioner. Previously, in the Center for Drug Evaluation, Dr. Murphy was Director of the Office of Counter-terrorism and Pediatric Drug Development (2001–2004), Associate Director for Pediatrics (1998–2001), and Director of the Office of Drug Evaluation with oversight for all of the divisions involved with

antimicrobial therapeutics (1998–2001). Dr. Murphy received her medical degree from the Medical College of Virginia. After completing a pediatric residency at the University of Virginia, she spent 3 years at the National Naval Medical Center as a Navy pediatrician before completing a fellowship in pediatric infectious diseases at the University of Colorado. Dr. Murphy was an Assistant Professor for Pediatrics at the University of Texas Health Science Center at San Antonio, an Associate Professor of Pediatrics and medical consultant to the Diagnostic Virology Laboratory at the University of Tennessee Medical Center at Knoxville, and Professor of Pediatrics and Chief of General Pediatrics at the University of Florida Health Science Center at Jacksonville. Dr. Murphy has numerous articles in refereed publications on pediatric infectious diseases, pediatric drug development, residency teaching, and laboratory diagnosis and is the editor of a book on office laboratory procedures.

Robert M. Nelson, MD, PhD, is currently Associate Professor of Anesthesiology and Critical Care at The Children's Hospital of Philadelphia (CHOP) and the University of Pennsylvania School of Medicine. After receiving his MD from Yale University in 1980, Dr. Nelson trained in pediatrics (Massachusetts General Hospital) and neonatology and pediatric critical care (University of California, San Francisco). He has received formal training in theology and religious and medical ethics, receiving a Master of Divinity from Yale Divinity School in 1980 and a PhD in The Study of Religion from Harvard University in 1993. Dr. Nelson has lectured and published widely on ethical and regulatory issues in pediatric research and clinical care. He is Chair of the Pediatric Advisory Committee (PAC) of the FDA, and former Chair of the PAC Pediatric Ethics Subcommittee. Dr. Nelson is a member of the Human Studies Review Board of the Environmental Protection Agency, and the Subcommittee on Research Involving Children of the Secretary's Advisory Committee on Human Research Protections, U.S. Department of Health and Human Services. He was a member of the IOM Committee on Clinical Research Involving Children (through March 2004), and former Chair of the AAP Committee on Bioethics (through 2001). Currently he is Director of the Center for Research Integrity, established at CHOP to further the responsible conduct of pediatric research. Dr. Nelson's current research explores different aspects of child assent and parental permission, such as adolescent risk perception, the development of a child's capacity to assent, and the degree to which parental choice is perceived as voluntary. His research has been funded by NIH, the Greenwall Foundation, and the National Science Foundation.

Walter A. Orenstein, MD, joined Emory University's School of Medicine in March 2004 as Director of a new Emory Program for Vaccine Policy and Development and as Associate Director of the Emory Vaccine Center. Dr. Orenstein retired from his 26-year career at the Centers for Disease Control and Prevention (CDC), where he led the National Immunization Program, a $1.6 billion effort with more than 450 staff, dedicated to reducing vaccine-preventable disease burdens around the world, including elimination of some of the greatest causes of childhood mortality and disability. Dr. Orenstein's primary appointment is in the Division of Infectious Diseases in the Department of Medicine at the Emory University School of Medicine. He holds faculty appointments in Pediatrics and in the Departments of International Health and Epidemiology in Emory's Rollins School of Public Health. During Dr. Orenstein's tenure at the National Immunization Program, he has led successful efforts to combat and markedly reduce the occurrence of once-common childhood diseases, including measles, rubella, mumps, meningitis from Haemophilus influenzae type b (Hib), varicella, and invasive pneumococcal disease. The Immunization Program also has made major contributions: protecting adults from vaccine-preventable diseases through eliminating barriers to vaccination and developing new vaccine strategies, expanding vaccine safety efforts, improving risk communication, and promoting the use of immunization registries.

William J. Rodriguez, MD, PhD, received his MD and his PhD in microbiology from Georgetown University. He completed his internship and residency at University Hospital in San Juan, Puerto Rico, and completed a fellowship in infectious disease at the Children's National Medical Center. He has been Professor of Pediatrics at The George Washington University (GWU) since 1985 and was Chairman of the Department of Infectious Diseases at Children's from 1983 to 2000. The author of more than 130 papers and book chapters, as well as numerous abstracts, Dr. Rodriguez has distinguished himself with his research in the areas of new antibiotic development, the treatment of middle ear infections, and the study of monoclonal antibodies in the prevention and treatment of respiratory syncytial virus in infants and young children. In 2000, Dr. Rodriguez retired from Children's National Medical Center and was appointed Professor Emeritus in GWU's School of Medicine and the Health Science. Dr. Rodriguez joined the FDA in July 2000, when he was appointed Science Director for Pediatrics in the Office of Counter-Terrorism and Pediatric Drug Development in the Center for Drug Evaluation and Research. He is currently the Science Director for Pediatrics in the Office of New Drugs in an assignment in the Office of Pediatric Therapeutics in the Office of the Commissioner. He has participated in the pediatric initiatives that have

encouraged pediatric drug development. Information from some of the initiatives' early findings has been communicated in scientific journals.

Wayne R. Snodgrass, MD, PhD, is a clinical pharmacologist, medical toxicologist, and pediatrician. He is the Medical Director of the Texas Poison Center–Houston/Galveston. He is Chair, AAP Committee on Drugs; Chair, Data Safety Monitoring Board of Pediatric Pharmacology Research Units, NICHD, NIH; Chair, Scientific Advisory Committee, American Association of Poison Control Centers; Chair, Neuroprotection Review Panel, U.S. Army; former Chair, Pediatric Expert Panel, U.S. Pharmacopeia; member, Best Pharmaceuticals for Children Act drug listing committee; member, Network Steering Committee, Obstetric Pharmacology Research Units, NICHD, NIH; member, Advisory Committee on Childhood Lead (Pb) Poisoning & Prevention, CDC; and former member, Non-Prescription Drug Advisory Committee, FDA. His clinical activities include Attending Physician for the clinical pharmacology–toxicology consult service at University Hospital Galveston; formerly Attending Physician for the pediatric intensive care unit; and formerly Attending Physician in the neonatal intensive care unit. His research interests include cytochrome P450 isozyme and allele patterns to predict individual toxicity risk for drugs that undergo metabolic activation; sedation and analgesia in infants and children; and development of drugs of choice criteria for use by physicians providing medical care for infants and children.

Stephen P. Spielberg, MD, PhD, has been Dean of Dartmouth Medical School since July 2003. He received an AB from Princeton University and an MD and a PhD (Pharmacology) from the University of Chicago. He did a pediatric internship and residency at Boston Children's Hospital and a fellowship in genetics at NICHD. He held faculty positions in pediatrics and in pharmacology at Johns Hopkins and the Hospital for Sick Children in Toronto, where he was a Director of Clinical Pharmacology and Toxicology. At Merck Research Laboratories and Johnson & Johnson, he was Vice President for Pediatric Drug Development prior to going to Dartmouth. He was Rapporteur for ICH E-11 and served on the FDA Pediatric Advisory Subcommittee while he was in industry. He is currently President of the American Society for Clinical Pharmacology and Therapeutics; on the Board of the Foundation for the NIH; on the Council of Convention of the U.S. Pharmacopeia; on the External Advisory Boards of the NICHD PPRU Network; and in the Elizabeth Glaser Pediatric Research Network.

Robert M. Ward, MD, completed medical school at Johns Hopkins University and trained in pediatrics, neonatology, and clinical pharmacology at the University of Minnesota. He was appointed to Assistant Professor

of Pediatrics and Pharmacology at Pennsylvania State University in 1979. His research interests focused on neonatal and fetal pharmacology and drug therapy. Dr. Ward moved to the University of Utah in 1985 as an Associate Professor of Pediatrics. He served as Medical Director of the Primary Children's Medical Center Newborn Intensive Care Unit from 1989 to 1997. He was promoted to Professor of Pediatrics in 1995. In 1997, he began the Pediatric Pharmacology Program at the University of Utah, a clinical trials program for the study of medications in children. He is currently PI of one of 13 sites in the NIH Pediatric Pharmacology Research Unit Network. In 1997, Dr. Ward became the Chair of the AAP Committee on Drugs and consulted in the development of the Food and Drug Administration Modernization Act, Best Pharmaceuticals for Children Act, and Pediatric Research Equity Act. He has consulted with the FDA and USP and testified before Congress regarding the study and approval of new drugs for pediatric patients. As a professor of pediatrics, he has authored more than 80 manuscripts, book chapters, and editorials.

Annic Weyersberg, MD, worked in the University Children's Hospital of Cologne before joining the European Agency for the Evaluation of Medicinal Products in November 2005 as a national expert for pediatrics for the preparation of the Paediatric Regulation.