Safe and Effective Medicines for Children

Pediatric Studies

Conducted Under the Best Pharmaceuticals for

Children and the Pediatric Research Equity Acts

NATIONAL RESEARCH COUNCIL
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Safe and Effective Medicines for Children:

Studies Conducted Under the Best Pharmaceuticals for Children Act and the Pediatric Research Equity Act

Committee on Pediatric Studies Conducted Under the Best Pharmaceuticals for Children Act (BPCA) and the Pediatric Research Equity Act (PREA)

Board on Health Sciences Policy

Marilyn J. Field and Thomas F. Boat, Editors

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

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The committee appreciates the contributions of the authors of the background papers and analyses that appear as Appendixes B, C, and D. We likewise appreciate the analyses conducted by staff of The Lewin Group (including Nancy Walczak, Ian Glen, and Cynthia Schuster) and their patience in discussing the details of these analyses, which changed extensively over the course of the project. Consultants Andrew Hershey and Charles Coté assisted with the analysis of studies and labeling changes involving migraine and anesthetic products. At the College of Pharmacy, University of Illinois at Chicago, Amy LoDolce was very helpful in initiating the work on what became Appendix D of this report.

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Reviewers

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

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Although the reviewers listed above have provided many constructive comments and suggestions, they were not asked to endorse the conclusions or recommendations, nor did they see the final draft of the report before its release. The review of this report was overseen by **Ellen Wright Clayton,** Vanderbilt University, and **Charles E. Phelps,** University of Rochester. Appointed by the National Research Council and the Institute of Medicine, these individuals were responsible for making certain that an independent examination of this report was carried out in accordance with the institutional procedures

and that all review comments were carefully considered. Responsibility for the final content of this report rests entirely with the authoring committee and the institution.

Preface

Children, in general, are healthier than their adult counterparts, particularly as adults reach the fifth decade of life and beyond. However, children do have multiple acute illnesses each year, and a substantial number of children, often estimated to be 20 percent or more, are burdened with chronic health disorders, some of them disabling or life threatening. Medical attention, including evidence-based prescription of drugs or biologics, is vital for their well-being.

In addition, children constitute a smaller percentage of the United States population than adults, so drugs are often designed for adults and initially tested and approved for use in adult populations. Clinicians, however, often begin to use these drugs—as is legal—with children without guidance from well-controlled clinical studies. Over time it has become apparent that pharmacologically, as well as in many other ways, children are not "small adults." In the 1980s and 1990s, policy makers, pediatricians, and others increasingly recognized the need to study the efficacy and safety of drugs in children. Key responses to that recognition—different policies that incentivize or require studies of drugs in children—are the focus of this report. The Best Pharmaceuticals for Children Act (BPCA) provides incentives for drug studies in children, and the Pediatric Research Equity Act (PREA) requires such studies in certain situations. Since the late 1990s, these policies (and their predecessors) have improved the availability of reliable information, which should, in turn, improve the appropriate use of therapeutic agents for children in clinical practice.

This Institute of Medicine (IOM) report, which was called for by Congress, documents improvements in the availability of evidence about the safety and efficacy of drugs in children following the adoption of these policies and their implementation by the Food and Drug Administration (FDA). It reflects the work of an IOM committee, representing a wide range of relevant expertise that worked diligently for more than a year to collect data on pediatric studies conducted under BPCA and PREA and to assess those data. The members of the committee engaged in lively debates and, in the end, came to conclusions that we believe will contribute to understanding and improving these policies and the pediatric studies prompted by them. For much of its work, the committee primarily relied on documents that were either posted on the FDA website (mostly documents issued after September 27, 2007) or supplied over a period of months by FDA after redaction (mostly documents issued earlier, before Congress required that they be made public).

Committee members poured through hundreds of pages of written requests and FDA clinical and other reviews to extract pertinent information. Thus, unlike many IOM committees, members both created and analyzed the data necessary to reach important conclusions. Also, unlike many other IOM committees, our committee was not asked to make recommendations, with one exception related to recently enacted policies to provide incentives for pediatric studies of biologics. The report was therefore constructed to transmit the conclusions of the committee's assessments of studies under BPCA and PREA, as well as conclusions from these assessments that might form the basis for future steps by FDA and Congress to build on the strengths and correct some of the shortcomings of these policies or their application.

The committee assessed the data from a spectrum of perspectives: pediatric, psychiatric, pharmacologic, ethical, legal, health policy, and consumer. The committee was assisted in this effort by a number of consultants and contributors to the task of assembling data for this review and sharing fresh insights. Importantly, the committee would like to recognize and express appreciation for the tireless leadership of our committee study director, Marilyn Field, and for the contributions of her staff colleagues, Claire Giammaria and Robin Parsell. It was their efforts that allowed the committee to evaluate and come to conclusions based on an enormous array of data. Above all, the committee hopes that its efforts will encourage ongoing scientifically and ethically sound study of drugs and biologics, particularly for children who are not yet advantaged by therapies demonstrated to be safe and effective for their medical conditions.

Thomas F. Boat, *Chair*
Committee on Pediatric Studies Conducted Under BPCA and PREA

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BOXES

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Abbreviations and Acronyms

AAP	American Academy of Pediatrics
ACR	American College of Rheumatology
ADHD	attention deficit hyperactivity disorder
AERS	Adverse Event Reporting System
AHA	American Heart Association
AHRQ	Agency for Healthcare Research and Quality
BLA	Biologics License Application
BPCA	Best Pharmaceuticals for Children Act
BPCIA	Biologics Price Competition and Innovation Act
CBER	Center for Biologics Evaluation and Research
CDC	Centers for Disease Control and Prevention
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CNS	central nervous system
COG	Children's Oncology Group
CYP	cytochrome P450
DESI	Drug Efficacy Study Implementation (FDA process)
DMC	data monitoring committee
DSI	Division of Scientific Investigations of the Center for Drug Evaluation and Research
EMA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDAMA	Food and Drug Administration Modernization and Accountability Act of 1997
FDC Act	Federal Food, Drug, and Cosmetic Act of 1938
FEV1	forced expiratory volume in 1 second
FOIA	Freedom of Information Act
GCP	good clinical practice
GERD	gastroesophageal reflux disease
HHS	U.S. Department of Health and Human Services
IBD	inflammatory bowel disease
IGIV	immune globulin intravenous

IM	intramuscular
IND	Investigational New Drug
IOM	Institute of Medicine
IRB	institutional review board
IV	intravenous
JIA	juvenile idiopathic arthritis
NDA	New Drug Application
NICHD	National Institute of Child Health and Human Development
NIH	National Institutes of Health
NME	new molecular entity
NRC	National Research Council
PAC	Pediatric Advisory Committee
PASI 75	75 percent or greater improvement from baseline in the psoriasis area and severity index
PD	pharmacodynamics
PDCO	European Union Pediatric Committee
PDR	*Physicians' Desk Reference*
PeRC	Pediatric Review Committee
PHS	Public Health Service
PIP	pediatric investigation plan
PK	pharmacokinetics
PPI	proton pump inhibitor
PREA	Pediatric Research Equity Act
SC	subcutaneous
TNF	tumor necrosis factor
UKHCDO	United Kingdom Hemophilia Center Doctors' Organization
UNC	University of North Carolina
WHO	World Health Organization

Summary

ABSTRACT

Beginning in the 1990s and continuing into 2010, the federal government has acted to increase the study of drugs in children and thereby reduce a serious deficit in the data on drug safety and efficacy for young patients. One step was to offer economic incentives for the conduct of pediatric studies. A second step was to require such studies in specific situations. These policies—in their current form, the Best Pharmaceuticals for Children Act (BPCA; which provides the incentives) and the Pediatric Research Equity Act (PREA; which provides the requirements)—seek to expand the information available to clinicians who prescribe medications to children and, as a consequence, to improve clinical care and health outcomes for children of all ages.

Consistent with legislative provisions adopted in 2007 and 2010, the Food and Drug Administration (FDA) asked the Institute of Medicine (IOM) to examine pediatric studies requested under BPCA (or its predecessor policies) or required under PREA (or its predecessor policies) and to consider the incentives for pediatric studies of biologics. A committee appointed by the IOM reviewed and assessed a representative sample of labeling changes and other FDA actions related to requested or required studies for the period from July 1, 1998, through December 31, 2010. The assessments covered the use of extrapolation and alternative endpoints for pediatric populations, neonatal assessments, ethical issues, and safety findings. The committee also examined the status of the incentives for pediatric studies of biologics created by the Biologics Price Competition and Innovation Act of 2009 (passed in 2010) and sought to identify and assess the importance of biological products that are not being tested for pediatric use. In the course of preparing its report, the committee reached several broad conclusions:

- *Pediatric studies conducted under BPCA and PREA are yielding important information to guide clinical care for children. Information from pediatric studies sometimes supports and sometimes runs counter to expectations about the efficacy, safety, and pharmacokinetics of a drug in children of different ages.*
- *Some studies requested under BPCA or required under PREA do not achieve their full potential. Reasons vary and may include the inability of sponsors to recruit sufficient numbers of children, the use of weak study designs and underpowered samples, the lack of dose-ranging studies to guide efficacy trials, and the omission of relevant study information from labeling. FDA has taken steps to address many of these problems.*

- *More timely planning, initiation, and completion of pediatric studies would benefit children. European requirements for the submission of plans for pediatric studies apply at a stage of drug development that may be somewhat premature, whereas U.S. requirements apply later than may be warranted. Delays in sponsor completion of required studies also warrant further attention.*
- *Pediatric drug studies remain particularly limited in certain areas, including the use of medications with neonates and the long-term safety and effectiveness of drugs for all pediatric age groups. The frequent lack of information about the long-term safety of drugs used with children is a special worry—both for drugs that may be used for decades for chronic conditions and for drugs for which short-term use may have adverse consequences on a child's development months or years later. Many drugs commonly used with premature and sick neonates are older drugs that have not been adequately evaluated in studies with this vulnerable age group.*
- *Congress has significantly expanded public access to information from recent pediatric studies conducted under BPCA and PREA and has thereby enhanced the value of these studies. Limitations still exist, however, particularly for products with PREA-related labeling changes that occurred prior to September 2007.*
- *The reauthorization processes for BPCA and PREA have improved policies promulgated under both acts, but frequent reauthorizations create uncertainties for industry and FDA.*
- *Pediatric studies of biologics conducted under PREA have generated valuable information. The 2010 expansion of BPCA to cover biologics has potential to expand knowledge further, but it is too early to assess its effects. Almost 90 percent of biologics that the committee investigated have been the subject of some study with children. Of the dozen biologics that have not been studied with children, most were approved for indications that are not diagnosed or very rarely diagnosed in children. Given the applicability to biologics of long-standing policies such as the 1984 Orphan Drug Act and PREA and given the range of existing pediatric research on many biologics, the incentives of BPCA may have a valuable but more modest effect in encouraging studies of biologics than they did for small-molecule drugs.*

The committee was not asked to make recommendations except with respect to pediatric studies of biologics. This report does, however, offer suggestions and options for Congress and FDA to

- *expand public access to information from pediatric studies conducted under BPCA and PREA;*
- *improve the timeliness of certain pediatric studies;*
- *strengthen pediatric studies requested under BPCA or required under PREA;*
- *address areas of limited pediatric investigation under BPCA and PREA; including neonatal studies and long-term safety studies;*
- *increase the clarity and understanding of FDA judgments about pediatric studies; and*
- *continue to encourage pediatric studies of biologics.*

In the late 1990s, the federal government took steps to increase the study of drugs in children and thereby reduce a serious deficit in the data on drug safety and efficacy for young patients. One step was to offer economic incentives for the conduct of requested pediatric studies. Another was to require such studies in specific situations. The objectives were to expand the information available to clinicians who prescribe medications to children and, as a consequence, to improve clinical care and health outcomes for children. These policies—in their current form, the Best Pharmaceuticals for Children Act (BPCA; which provides the incentives) and the Pediatric Research Equity Act (PREA; which provides the requirements)—are the focus of this report from a committee of the Institute of Medicine (IOM).

BPCA and PREA are implemented by the Food and Drug Administration (FDA), which must approve drugs before they can be legally marketed in the United States. Drugs that have been approved and labeled on the basis of studies only with adults may be legally prescribed for children as part of the practice of medicine. For clinicians who prescribe drugs for children, evidence from pediatric studies is critical

- to understand age- and development-related variations in the way that the body affects a drug (i.e., the drug's pharmacokinetics, including absorption, distribution, metabolism, and excretion) and in the way that a drug affects the body (i.e., its pharmacodynamics);
- to develop evidence about age- and development-related variations in a drug's short- and long-term efficacy and safety; and
- to evaluate, when necessary, a developmentally suitable formulation of a drug (e.g., an oral solution for toddlers who cannot swallow tablets).

The results of drug studies with children may differ from the results of studies with adults, revealing, for example, a different profile of adverse events. Studies may also guide dosing adjustments that are often more complicated than simply scaling down doses recommended for adults on the basis of a child's age or weight.

The shortage of pediatric drug studies that prompted passage of BPCA and PREA (and their predecessor policies) can be traced to many factors—in particular, the fact that children constitute a small market for medications compared with the market constituted by adults. Moreover, pediatric drug studies are often challenging. Study strategies used with adults may require adaptations to accommodate both the small numbers of potential child research participants and the developmental differences between children and adults. If a product is already approved for marketing to adults and thus available for off-label use, study sponsors may find that clinicians and parents are reluctant to enroll a child in a trial, especially a placebo-controlled trial. In addition, studies must follow federal rules that limit the participation of children in certain types of studies that are considered ethical for adults.

Both BPCA and PREA use the term *pediatric*, but neither the statute nor implementing regulations define the age range to which it applies. FDA definitions vary, but, in general, the pediatric population consists of children from birth up to 16 or 17 years of age. When requesting or requiring pediatric studies, FDA typically tailors the

specification of included age groups to the characteristics of the condition and drug to be studied.

STUDY ORIGINS AND FOCUS

Consistent with provisions of the 2007 law reauthorizing BPCA and PREA and with provisions of the Biologics Price Competition and Innovation Act (BPCIA) enacted in 2010, FDA asked the IOM to examine pediatric studies requested under BPCA or required under PREA. The tasks for the committee appointed by the IOM were:

1. Review and assess a representative sample of written requests issued by the Secretary [of the U.S. Department of Health and Human Services] and studies conducted under BPCA since 1997, and labeling changes made as a result of such studies.
2. Review and assess a representative sample of studies conducted since 1997 under PREA or precursor regulations, and labeling changes made as a result of such studies.
3. Using a representative sample of written requests issued by the Secretary and studies conducted under BPCA since 1997 and studies conducted since 1997 under PREA or precursor regulations, review and assess (a) the use of extrapolation for pediatric subpopulations; (b) the use of alternative endpoints for pediatric populations; (c) neonatal assessment tools; and (d) ethical issues in pediatric clinical trials.
4. Using a representative sample of studies conducted since 1997 under PREA or precursor regulations, review and assess the number and type of pediatric adverse events.
5. Review and assess the number and importance of biological products for children that are being tested as a result of the amendments made by the Biologics Price Competition and Innovation Act of 2009 [passed in 2010] and the importance for children, health care providers, parents, and others of labeling changes made as a result of such testing.
6. Review and assess the number, importance, and prioritization of any biological products that are not being tested for pediatric use.
7. Offer recommendations for ensuring pediatric testing of biological products, including consideration of any incentives, such as those provided under section 505A of the Federal Food, Drug, and Cosmetic Act or section 351(m) of the Public Health Service Act.

Because BPCA did not take effect until July 1, 1998, and because documents associated with drug approvals are not immediately made public by FDA, the committee's sample of written requests and other documents and actions covered the period from July 1, 1998, to December 31, 2010. For this period, FDA supplied a master list of labeling changes categorized by major therapeutic area and policy origin (BPCA, PREA, or their predecessor policies). From this list, the committee selected a sample of 46 FDA actions (for 44 distinct products) representing these therapeutic and policy categories. The committee excluded vaccines (which are subject to additional public oversight and needs assessments) and contraceptives (which are routinely approved without new pediatric studies). With these exclusions, the universe included

approximately 380 labeling changes. The committee also reviewed additional FDA actions involving written requests, studies with neonates, and, to the extent possible, required pediatric studies of biologics.

FDA's list of labeling changes excludes some labeling changes for biologics (including vaccines) that were approved before September 27, 2007, and FDA was unable to supply the missing information. Therefore, the committee's sample underrepresents biologics to an unknown degree.

For product approvals issued before September 2007, Congress has not required that relevant documents be made public. FDA did, however, agree to provide such documents for selected products after redaction of confidential information. Because the documents that companies submit to FDA are not public, the committee's assessments relied primarily on FDA staff reviews of these materials.

This report profiles the results of the committee's analyses of requests, requirements, studies, and labeling changes associated with BPCA and PREA. In the course of preparing the report, the committee reached several broad conclusions.

- *Pediatric studies conducted under BPCA and PREA are yielding important information to guide clinical care for children.* The yield varies by medical condition, type of product, and age group. Information from pediatric studies sometimes supports and sometimes runs counter to expectations about the efficacy, safety, and pharmacokinetics of a drug in children of different ages.
- *Some studies requested under BPCA or required under PREA do not achieve their full potential.* Reasons vary and may include the inability of sponsors to recruit sufficient numbers of children, the use of weak study designs and underpowered samples, the lack of dose-ranging studies to guide efficacy trials, and the omission of relevant study information from labeling. FDA has taken steps to address many of these problems.
- *More timely planning, initiation, and completion of pediatric studies would benefit children*. European requirements for the submission of plans for pediatric studies apply at a stage of drug development that may be somewhat premature, whereas U.S. requirements apply later than is needed for access to safety and efficacy data from adult studies that are sufficient to support the planning and initiation of pediatric studies. Delays in sponsor completion of studies required under PREA also warrant further attention.
- *Pediatric drug studies remain particularly limited in certain areas, including the use of medications with neonates and the long-term safety and effectiveness of medications used for all pediatric age groups.* The lack of information about the long-term safety of drugs prescribed for children is a special worry—both for drugs that may be used for decades for chronic conditions and for drugs for which short-term use may have adverse consequences on a child's development months or years later. Many drugs commonly used with premature and sick neonates are older drugs that have not been adequately evaluated in this vulnerable age group.
- *Congress has significantly expanded public access to information from recent pediatric studies conducted under BPCA and PREA and has thereby enhanced the value of these studies.* Limitations still exist, however, particularly for older pediatric studies and labeling changes.

- *The reauthorization processes for BPCA and PREA have improved policies promulgated under both acts, but frequent reauthorizations create uncertainties for industry and FDA.* Since 1997, Congress has strengthened the application of pediatric expertise to studies conducted under BPCA and PREA, has directed that information from pediatric studies be added to product labeling in most cases, and has required a follow-up assessment of adverse event reports for the first year following a labeling change. Nonetheless, the frequent reauthorizations of the two acts—every 5 years—create uncertainties for companies, given the typically long lead time required to plan and conduct studies.
- *Requirements for pediatric studies of biologics conducted under PREA have generated valuable information. The 2010 expansion of BPCA to cover biologics has potential to expand knowledge further, but it is too early to assess its effects.* Almost 90 percent of biologics that the committee investigated have been the subject of some study with children.[1] Of the dozen biologics that have not been studied with children, most were approved for conditions that are not diagnosed or very rarely diagnosed in children. Given the applicability of long-standing policies such as the 1984 Orphan Drug Act and PREA and given the range of existing pediatric research on many biologics, BPCA may have a valuable but more modest effect in encouraging studies of biologics than was the case for small-molecule drugs.

Except with respect to recent incentives for pediatric studies of biologics, the committee was not asked to make recommendations. This report does, however, include suggestions and options for Congress and FDA in several areas, as discussed below.

POLICIES TO PROMOTE STUDIES OF DRUGS IN CHILDREN

Beginning in the early 1900s with the deaths of children due to unsafe vaccines and continuing with more deaths due to unsafe anti-infectives in the 1930s and 1950s, public dismay about harms to children contributed to the passage of federal laws intended to promote drug safety and efficacy. Ironically, these laws—which range from the Biologics Control Act of 1902 to the Food, Drug, and Cosmetic (FDC) Act of 1938 and the 1962 Kefauver-Harris amendments to the FDC Act—did not encourage or direct studies of medication safety and efficacy in children. Not until 1997 did Congress or FDA adopt incentives and requirements for such studies.

Best Pharmaceuticals for Children Act

Among other provisions, the Food and Drug Modernization and Accountability Act of 1997 offered companies pediatric exclusivity—a period of marketing protection from competitor (generic) drugs—when they undertook pediatric studies of a drug based

[1] Somewhat simplified, a *drug* is a substance other than a food or medical device that is intended to affect the body's structure or functioning or to diagnose, treat, or prevent disease. A *biologic* is a drug derived from human or animal sources or microorganisms. Examples of biologics include vaccines, blood or blood products, allergens, and recombinant therapeutic proteins (with certain exceptions).

on a written request from FDA. This exclusivity extends for 6 months beyond any existing period of marketing protection because of patents or other types of exclusivity.

When granted, pediatric exclusivity applies to all forms of a company's drug that contain the same active moiety or ingredient. For a drug with a lucrative market among adults, this added period of marketing protection is economically significant. Exclusivity is available when a company meets the terms of FDA's request, whether or not the results support pediatric use, because information about a drug's lack of efficacy or safety is as important as positive findings.

Pediatric exclusivity is generally not relevant to drugs that have no existing exclusivity or remaining patent life. Thus, in 2002, Congress directed the National Institutes of Health (NIH) to create a pediatric drug development program under BPCA and to set priorities for pediatric studies of off-patent drugs (a task that has since been expanded to cover pediatric therapeutics broadly). Under this program, NIH has supported the study of several high-priority off-patent drugs.

Congress reauthorized the exclusivity incentive in 2002 (under the BPCA title) and again in 2007. BPCA is due for reauthorization in October 2012.

Pediatric Research Equity Act

In 1998, FDA issued regulations generally referred to as the Pediatric Rule. Except when FDA waived or deferred its application, the rule required that companies seeking approval of a New Drug Application (NDA) or Biologics License Application (BLA) include a pediatric assessment of the product if the submission involved a new active ingredient, indication, drug form, dosing regimen, or route of administration. The rule went into effect on April 1, 1999. After opponents successfully challenged the rule in court, Congress codified its key features in the Pediatric Research Equity Act of 2003. Like BPCA, PREA was reauthorized in 2007 and is next due for reauthorization in 2012.

PREA does not cover drugs designated under the Orphan Drug Act and applies only to the indications approved for an NDA or BLA. It permits FDA to waive required studies with some or all pediatric age groups, for example, if studies would be infeasible because the indication in question does not occur in children or evidence suggests that pediatric use of the drug would be unsafe. FDA often defers pediatric studies because the manufacturer has completed studies to support approval for use by adults.

One concern for companies is variation between the United States and Europe in requirements for pediatric drug studies. Oversimplified, the European Medicines Agency requires submission of a pediatric study plan early during the clinical investigation of a drug in adults, whereas the United States requires the plan late in the drug approval process. Although harmonization of the policies would require action by both Congress and European authorities, *Congress could act independently to require the more timely submission of pediatric plans in the United States after the completion of Phase II studies with adults.*

Congress has made PREA and BPCA more consistent in certain respects. It has expanded public access to information from pediatric studies under both policies. In addition, an internal committee with pediatric expertise (the Pediatric Review

Committee) must now review written requests authorized under BPCA and deferrals and waivers of PREA requirements.

ETHICAL ISSUES IN PEDIATRIC DRUG STUDIES

One broad ethical principle for the conduct of pediatric drug studies is that children should not be subjected to research that is not necessary to advance knowledge that is relevant to child health. Another is that children should not participate in studies that are designed or conducted in ways that predictably undermine the potential of the research to generate valid and useful information.

In reviewing ethical issues in pediatric clinical trials conducted under BPCA and PREA, the committee recognized that a number of safeguards are in place to prevent unethical clinical studies with children. These safeguards include federal regulations and international standards for research conduct and systems for research review and monitoring. The safeguards also provide for the application of pediatric expertise (including expertise in pediatric ethics) to FDA's activities under BPCA and PREA.

Most clinical reviews that the committee examined included brief comments on ethics, data integrity, and financial disclosures. Nonetheless, FDA clinical and other reviews generally do not provide details sufficient for the external assessment of certain important aspects of research conduct, for example, the adequacy of research protections at foreign research study sites or the processes for securing parental permission for or child assent to research participation.

One issue identifiable in the committee's sample involves placebo-controlled pediatric trials. Approximately half of the products were studied with a placebo control, and some of these studies involved conditions (e.g., asthma) for which effective therapies exist. Such trials do not necessarily present ethical problems, but *the committee suggests that FDA's written requests and clinical reviews describe the scientific and ethical rationales for the use of such trial designs.*

Another issue is that despite substantial improvements in public access to information, limitations continue, for example, as a result of the lack of access to reviews of older studies and the redaction of key sections of clinical reviews. In addition, the lack of integration of FDA reviews of pediatric (and adult) studies into resources such as Medline means that these detailed evaluations and analyses may not be identified and incorporated into evidence-based reviews of clinical therapeutics. *Congress could further improve access by directing FDA to make public reviews for labeling changes approved before September 2007 and to identify all PREA-related labeling changes for biologics. It could also request an independent evaluation of the extent and appropriateness of redactions in FDA reviews of pediatric studies and ask FDA to explore the integration of clinical and other reviews into databases such as PubMed and ClinicalTrials.gov.* To obtain a better understanding of the dissemination of information, *FDA could seek an analysis of third-party dissemination of labeling information from studies conducted under BPCA and PREA, including both the speed of dissemination and the accuracy and completeness of the information as disseminated.*

The committee recognized FDA's limited resources. At the same time, it was concerned that rationales for ethically and scientifically sensitive decisions be clear and

that the public have access to information in which sponsors, investigators, research participants, taxpayers and health insurance premium payers, and FDA staff have already invested—in different ways—considerable expense or effort.

The task for IOM did not include evaluation of the ethics of pediatric marketing exclusivity itself, but the committee acknowledges that issues such as intergenerational justice (e.g., higher costs for drugs used by older adults during the period of marketing protection) warrant attention. Certainly, it is appropriate that written requests be accompanied by clear expectations that the requested studies are necessary, soundly designed and executed, and public in their results.

SAFETY AND EFFICACY IN STUDIES CONDUCTED UNDER BPCA AND PREA

The IOM was asked to assess the number and type of pediatric adverse events in a sample of studies conducted under PREA or precursor regulations. FDA defines adverse events as any "untoward medical occurrence[s] associated with the use of a drug in humans, whether or not considered drug related." FDA reviewers provide detailed assessments of adverse event data that sponsors submit and typically judge a substantial proportion of reported events to be unrelated to the study drug.

Because adverse events often are not drug related, the IOM committee decided that it would not be productive to review and assess the number and type of adverse events in pediatric studies. Instead, the committee focused on clinical reviewers' more general and relevant conclusions about a product's safety signal or profile, such as whether the safety issues identified in pediatric studies were similar to those found in adult studies (for products that had been studied in adults) or to those identified for similar products. Because reviews of safety data are important for studies conducted under BPCA, the committee's sample also included such reviews.

Particularly for recent years, the committee found that FDA reviewers were generally thorough in evaluating adverse events, assessing their significance, and reaching conclusions about the safety profile of drugs studied with children. Summaries of conclusions about safety were usually accompanied by discussions of serious drug-related adverse events and the possible need for changes in the safety elements of a product's labeling.

To further improve the completeness, consistency, and clarity of safety assessments in clinical reviews, *the committee suggests that FDA's Center for Biologics Evaluation and Research explicitly adopt a template for clinical and other reviews similar to that used by the Center for Drug Evaluation and Research*. Many reviews are long and detailed; readers benefit from clear summary conclusions about a product's efficacy, safety profile, significant adverse events, and risks weighed against benefits.

The 1-year reviews mandated by Congress provide useful opportunities for FDA to examine safety information after labeling changes based on pediatric studies have been made and, in some cases, to recommend further analyses or inclusion of additional safety findings in product labeling. Given the limitations of the short-term studies typically used to support labeling changes and the limitations of the 1-year reviews, *FDA might*

consider more frequent use of its authority to require sponsors to undertake long-term postmarket, follow-up studies of serious or potentially serious risks to patient safety.

With respect to efficacy, IOM was asked to assess the use of alternative endpoints and extrapolation. The committee defined *alternative endpoints* in pediatric studies to be measures of efficacy that take children's growth and development into account and thus differ from endpoints for the same or a highly similar condition in adult studies. Alternative endpoints may be used for a variety of reasons. For example, use of an endpoint consisting of a symptom self-report measure would not be appropriate for preverbal children.

Approximately half of the primary efficacy endpoints used in the pediatric studies that the committee examined were the same as those used in adult studies, roughly one-fifth were alternative endpoints, and most of the remainder involved conditions found primarily or entirely in children. Although most alternative endpoints appear to be reasonable, *it would be desirable for FDA to include an explicit discussion of their use (including whether they had been validated for use with the age groups to be studied) in written requests and clinical reviews.*

To approve the labeling of drugs for pediatric use, FDA and companies have relied extensively on the extrapolation of efficacy from studies conducted with adults or, less often, other pediatric age groups. For almost half of the labeling changes in the committee's sample resulting from studies conducted under BPCA and PREA, the agency was prepared to accept what it terms partial extrapolation of efficacy based on submission of one controlled pediatric safety and efficacy study plus pharmacokinetic data. For almost 60 percent of such submissions, FDA approved labeling for pediatric use. For another third of the committee's sample, the agency was not willing to accept extrapolation but required two well-controlled studies; it approved pediatric labeling for almost half of these submissions. In other cases, FDA was prepared to accept extrapolation with the submission of pharmacokinetic and safety data and limited data on efficacy. Compared with an agency staff analysis that was limited to studies requested under BPCA, the committee's sample included a higher proportion of submissions for which no extrapolation was acceptable and a lower proportion of submissions for which complete extrapolation was acceptable (on the basis of additional pharmacokinetic and safety data only).

FDA reviews typically provide limited rationales for the use of extrapolation, and the law requires only brief documentation. Given the extent and significance of FDA's reliance on extrapolation of efficacy, *it would be desirable for agency written requests and clinical reviews to offer the public a somewhat fuller justification than is now provided when the agency accepts complete or partial extrapolation*. Again, the committee recognized that provision of such justifications or explanations adds to the demands on agency staff.

NEONATAL ASSESSMENTS

In considering how to interpret the term *neonatal assessment tools* as used but not defined in the statement of task, the committee decided to examine neonatal assessments, that is, clinical studies of drugs in neonates, generally. FDA provided the committee with

a list of products for which information from studies with neonates had resulted in labeling changes or awards of exclusivity without labeling changes. From 1998 through 2010, only 23 of the more than 350 labeling changes resulting from new pediatric studies included information from studies with neonates. Another five products had been studied in neonates and companies had received exclusivity, but no information from the neonatal studies was added to the labeling.

In the requests and requirements for studies that the committee examined, the age groups covered by waivers typically were not limited to neonates but covered a broader age range, for example, children less than 3 years of age. The conditions covered by the waivers, for example, autism and asthma, are either rare or not diagnosed in children less than 1 month of age.

Several factors appear to increase the likelihood that requests or requirements for studies with neonates will generate useful information. They include clarity about the nature of the condition to be studied, valid and reliable methods to diagnose it, and, for studies of response or efficacy, valid and reliable endpoints. In requesting or requiring studies with neonates, it is important that FDA consider the state of current knowledge about the diagnosis and the availability of valid and reliable endpoints for neonates, as well as the seriousness and frequency of the disease in question.

A review of data on medications commonly used by neonates suggests that they are typically older, off-label products for which pediatric exclusivity is not available. *To promote more studies of drugs widely used but not adequately evaluated in neonates, one option is for Congress to provide additional resources for short- and long-term neonatal drug studies through the BPCA program at NIH.*

OUTCOMES OF WRITTEN REQUESTS AND PREA REQUIREMENTS

Overall, from July 1998 through October 2011, FDA approved more than 420 labeling changes associated with studies requested under BPCA or required under PREA (or their predecessor policies). Some changes did not involve new pediatric trials, and FDA's count omits labeling some changes for biologics that occurred before September 27, 2007. As of October 2011, FDA had also

- issued more than 340 written requests under BPCA, nearly half of them in the first 2 years of the program;
- approved nearly 150 labeling changes solely as a result of requested studies and granted exclusivity to more than 175 active moieties;
- approved at least 180 labeling changes solely as a result of studies required under PREA;
- approved 50 labeling changes as a result of studies both requested under BPCA and required under PREA; and
- made public the clinical and other reviews associated with 139 labeling changes that had been made since September 2007.

Most written requests that FDA has issued (approximately 80 percent) have been proposed by sponsors rather than initiated by FDA. Roughly half of written requests have

led to the submission of pediatric studies for which exclusivity was granted, and more such studies will be submitted in the future.

The number of written requests issued by year peaked at more than 90 in 1999 and then dropped sharply, with a more recent leveling off to approximately a dozen requests per year. The number of grants of exclusivity rose fairly steadily for the first several years, reaching almost 60 in 2008 and then dropping steeply. Of the written requests that the committee examined, the general pattern has been for the types of trial designs and sampling strategies described in requests to become more specific and rigorous over time. The health benefit expected from requested studies is, however, rarely described or justified. *It would be desirable for FDA to more clearly articulate the health benefits expected of requested studies so that children do not participate in requested studies of minimal value.*

PREA has become increasingly important as a source of pediatric studies. From 2008 through 2010, more than 60 percent of labeling changes were attributable solely to PREA requirements and another 22 percent were attributable to both BPCA and PREA.

One concern is delays in studies required under PREA, and another is that FDA has limited practical ability to require their completion. An option for *Congress is to provide FDA with more flexibility to impose sanctions, including monetary penalties, for unreasonably delayed studies.*

Most studies that the committee reviewed generated useful information about efficacy and safety, including information about products that were widely used off-label. The majority led to the labeling of a product for use by some pediatric age groups. Some studies, however, yielded unexpected findings about safety or efficacy and led to recommendations against use by children.

Some studies had weaknesses in their design or their execution that modestly or significantly limited their value. Shortcomings involved the specification of endpoints inappropriate for some age groups, weak trial designs, inadequate sampling strategies, and inadequate investigations to identify an effective dose of a study drug. FDA has recognized the importance of developing data to guide the selection of appropriate doses for efficacy studies, but *the need for strict and consistent attention to dose selection for evaluation in pediatric drug studies remains.*

The committee's review indicates that FDA has improved its specification of trial designs in requests and requirements for pediatric studies. In the future, its regulatory science initiatives should support further improvements, as should a number of activities that the agency has undertaken to evaluate specific challenges in pediatric trial design and propose innovative strategies to meet these challenges. *To improve pediatric studies of drugs and biologics and their evaluation, it is important for FDA to continue to expand initiatives to strengthen the science base for its work, analyze shortcomings in pediatric studies, and develop innovative strategies to meet the specific challenges of pediatric trials.*

Just as most studies requested under BPCA or required under PREA yielded useful information, most labeling changes reflected this result. However, labeling changes have sometimes excluded or downplayed important information, for example, information about certain adverse events. In a few cases, labeling changes were ambiguous or internally contradictory, recommending against pediatric use but also providing information to guide pediatric dosing. These situations may illustrate the

dilemma that FDA faces when studies do not show efficacy but the agency expects off-label use to continue. It is important that FDA be clear that the provision of information about pediatric dosing in such situations does not constitute a recommendation for pediatric use. *The agency can use transitions to the current, structured labeling format to clarify ambiguous, incomplete, or contradictory pediatric information in earlier labeling*.

PEDIATRIC STUDIES OF BIOLOGICS

With some limitations, Congress extended the incentives of BPCA to biologics in 2010. FDA still has many complex questions to consider in implementing BPCIA. Even after it issues regulations, it will take time for the agency to prepare specific written requests, for willing sponsors to conduct and submit requested studies, and then for FDA to evaluate the submissions and make its judgments public. Given these constraints, the committee concluded that it was too early either to assess the impact of BPCIA on pediatric studies of biologics or to reach conclusions about its effectiveness or its limitations in ensuring pediatric studies of biologics. *Thus, it is reasonable for Congress to continue the extension of BPCA to biologics until the results can be systematically evaluated 3 to 5 years after FDA issues implementing regulations.*

Barring surprises in their implementation, the incentives of BPCIA can be expected to encourage further pediatric studies of both older and newer biologics. Nonetheless, it seems unlikely that the law will lead to a surge of written requests for pediatric studies of biologics similar to the surge in requests for pediatric drug studies that followed the creation of the pediatric exclusivity incentive in 1997. Since 1999, biologics have been subject to PREA requirements (with exemptions for orphan-designated drugs). In addition, biologics have been eligible for the incentives of the Orphan Drug Act, which offer 7 years of exclusivity. Nearly three-quarters of the 390-plus orphan drug and biologics approvals since 1984 have involved rare conditions that affect children.

Whether as a result of PREA, the Orphan Drug Act, the evident therapeutic promise of many biologics, or other factors, approximately 60 percent of the 97 still-marketed biologics (excluding vaccines, assays, and reagents) that FDA has approved since 1997 are labeled for pediatric use, have some information about pediatric studies in the labeling, or have warnings against pediatric use based on analysis of postmarket safety reports. Further, an examination of studies registered at the ClinicalTrials.gov database indicates that most of the remaining products have been studied, are being studied, or are planned for studies with children. Of the dozen biologics that have not been studied with children, most appear either to have limited potential to benefit children or to be in the same class as alternative products that are labeled for pediatric use. On the basis of case reports of off-label use and other information, the committee identified one product that may have sufficient promise for treating refractory infantile hemangiomas that FDA or NIH, or both, might consider encouraging or supporting controlled pediatric trials of its safety and efficacy.

The committee's finding that most biologics have been studied with children does not mean that no further opportunities or needs for pediatric studies of these medications exist. Such opportunities could include studies that pursue promising findings in early-

phase studies of specific biologics or studies of biologics for treatment of conditions that are now recognized to occur more frequently in children than previously thought.

1
Introduction

In the late 1990s, the federal government enacted policies to expand the study of drugs in children and thereby to begin to correct a serious deficit in the data on drug safety and efficacy for young patients. In one case, it offered marketplace incentives for the completion of pediatric drug studies. In the other case, it required such studies in specific situations. The objectives of these policies were to expand information for clinicians who prescribe drugs to children and, as a consequence, to improve pediatric clinical care and child health outcomes. These policies—in their current form, the Best Pharmaceuticals for Children Act (BPCA; which provides the incentives) and the Pediatric Research Equity Act (PREA; which provides the requirements)—are the focus of this report from a committee of the Institute of Medicine (IOM).

BPCA and PREA are implemented by the Food and Drug Administration (FDA), which must approve new drugs before they can be legally marketed in the United States. Drugs that have been approved and labeled on the basis of the results of studies conducted with adults may be legally prescribed by health care professionals (as part of the practice of medicine) for children.[1] Clinicians who treat young patients often have had to prescribe medications without specific, scientific information on their safe and effective use by children of different ages and sizes. This "off-label" prescribing may be guided by the personal experience as well as the accumulated experience of clinicians, which may be published in the medical literature as case series reports or codified in consensus guidelines. Although recent years have seen increasing emphasis on evidence-based practice guidelines, neither guideline developers nor practitioners can use evidence that does not exist or is not public. The use of medications by children without guidance from pediatric studies of safety and efficacy raises ethical issues that underscore the importance of such studies. In some cases, high-quality clinical trials sponsored by government agencies or nonprofit groups are available but are not reflected in product labeling.

In the years preceding the adoption of BPCA and PREA and their predecessor policies, several analyses documented the lack of information on the safety and efficacy of FDA-approved medications that are prescribed for children. Table 1-1 summarizes several of these.

[1] Manufacturers may not promote and are limited in their ability to disseminate information about product uses for which they have not obtained FDA approval.

TABLE 1-1 Historical Data on Drugs Without Adequate Labeling for Pediatric Use

Year	Extent of Pediatric Drug Labeling
1973	78% of drugs listed in the *Physicians' Desk Reference* (PDR) lacked sufficient pediatric drug labeling
1984–1989	80% of new molecular entities (NMEs) approved by FDA lacked pediatric drug labeling
1991	81% of drugs in PDR had disclaimers or age restrictions
1991	44% of NMEs with potential pediatric usefulness had no pediatric labeling when approved
1992	79% of NMEs were not approved for potential pediatric use
1991–1994	71% of NMEs lacked pediatric drug labeling
1996	37% of NMEs with potential pediatric usefulness had some pediatric labeling when approved

SOURCE: Adapted from Wilson (1999), with additional information from FDA (1998).

The frustration of many clinicians with the lack of pediatric prescribing information was expressed decades ago in a 1968 editorial in the *Journal of Pediatrics* that referred to children as "therapeutic orphans" (Shirkey, 1968). This oft-used description of children appeared years later in the Senate report (Senate Report 105-43, 1997) that accompanied the Food and Drug Administration Modernization and Accountability Act of 1997 (FDAMA; PL 105-115). FDAMA first established the incentives for pediatric research, which were reauthorized in 2002 and 2007. The 1997 Senate report also stated that less than 20 percent of prescription medications available in the United States were labeled for pediatric use.

For drugs that may be used by children as well as adults, evidence from pediatric studies is important for several reasons (see, e.g., IOM, 2000, 2008; Kearns et al., 2003, Reed and Gal, 2004; Ward and Lugo, 2005; Rakhmanina and Van Den Anker, 2009). These include the need to

1. understand age- and development-related variations in the way that the body affects a drug (pharmacokinetics, including absorption, distribution, metabolism, and excretion);
2. identify age- and development-related variations in how a drug affects the body (pharmacodynamics);
3. develop evidence about age- and development-related variations in a drug's short- and long-term benefits and harms (efficacy and safety); and
4. provide the basis for creating developmentally suitable formulations of a drug (e.g., an oral solution for a toddler who cannot swallow a pill or capsule).

Several factors, notably economic disincentives, explain the historical shortage of pediatric drug studies and the need for BPCA and PREA (see, e.g., IOM, 2000, 2008; Milne, 2009). Children, who account for approximately 25 percent of the nation's population, are usually healthy (FIFCFS, 2009). They provide a far smaller market for most medications than do adults, especially older adults. Even for common childhood conditions such as asthma, individuals age 18 years or older account for 75 percent of those with the condition (Akinbami, 2006). Drug studies with adults thus typically offer

companies a better economic return on their research investment than do pediatric studies. Even when pediatric studies result in positive findings and labeling of a drug for pediatric use, companies may not recover the costs of the research.

Moreover, the study of a drug in children may be more challenging than the study of the same drug in adults. Recruitment of a sufficient number of children may require more study sites. That difficulty is multiplied to the extent that studies need to include sufficient numbers of children in different age groups to support credible conclusions about safety, efficacy, and dosing across the developmental spectrum. Although pediatric studies may include a smaller total number of participants, sponsors still incur many of the same fixed research costs that they do for larger adult studies.

Even with multiple sites, pediatric studies sometimes cannot be completed because investigators are unable to secure an acceptable sample size in a reasonable period of time. Also, if FDA is requesting or requiring studies of several drugs in the same class or for the same condition, companies may be competing with each other for the same pool of child research participants. In addition, as noted above, once a drug is approved for use by adults, clinicians can legally prescribe it for children. This availability may discourage physicians and parents from enrolling children in a trial of the drug. Companies thus benefit from sales of the drug without the necessity of conducting studies to demonstrate the safety and efficacy of pediatric use.

Beyond limited numbers, companies and investigators may encounter other problems of practicality or feasibility. Young children may lack the developmental maturity to cooperate with certain research procedures or measurements. For children too young to reliably swallow existing tablet or capsule forms, a new formulation may be required, and development of such a formulation adds time and costs to pediatric studies.

Ethical considerations also complicate pediatric research. Reflecting concerns that date back to the 1960s and before, the federal government in 1983 added special protections for children to federal regulations on the ethical conduct of human research (21 CFR 50 Subpart D; see also IOM, 2004). For example, parents normally must give their permission for their child's participation in research. As discussed further in Chapter 4, certain studies that are required to support approval of a drug for adult use—notably, early studies with healthy individuals to understand a drug's pharmacokinetics—may be unethical to undertake with healthy children and also impermissible under federal regulations, except under limited conditions.

Notwithstanding these complexities, the study of drugs in children is essential because children's growth and development affect their responses to medicines. Fortunately, public officials, investigators, and manufacturers have demonstrated a commitment to expanding research on the safety and efficacy of drugs in children. Such research has contributed important information to guide the prescribing of drugs for children (Box 1-1).

BOX 1-1
Knowledge Contributed by Pediatric Drug Studies Conducted Under BPCA and PREA

Pediatric studies support safety and efficacy
Insulin glulisine (Apidra), a recombinant, rapid-acting human insulin analog, was approved in 2004 for treatment of type 1 diabetes mellitus in adults, with a requirement for a study with children ages 5 to 17 years (Meyer, 2004). In 2008, on the basis of the findings of one previously submitted pharmacokinetic/pharmacodynamic study and one new safety and efficacy study, FDA approved use of the product by children ages 4 to 17 years, the period of peak onset for this disease (Gabry and Joffe, 2008).

Safe and effective dosing in children differs from expectations
Gabapentin (Neurontin) was first approved in 1993. FDA requested studies under BPCA in 1999, and the drug was approved in 2000 as adjunctive treatment of partial seizures in children ages 3 years and older (Katz, 2000). Based on staff analyses of pharmacokinetic data, FDA concluded that children under 5 years of age required higher than anticipated doses (Feeney, 2000). Findings from the study for the 3- to 12-year-old age group also led to a warning on the product's label about adverse neuropsychiatric events, such as concentration problems, hostility, and hyperactivity.

Drug affects growth and development
Pegylated interferon alfa 2b (PegIntron) in combination with ribavirin (Rebetol) was approved in June 2008 for the treatment of chronic hepatitis C virus infection in patients ages 18 years or older, with deferral of PREA-required studies for children ages 3 years or older. In December 2008, after the required studies were submitted, FDA approved labeling for use by that age group. The clinical review noted that "growth inhibition and hypothyroidism were two notable adverse reactions" and that they were being further evaluated in a 5-year follow-up study (Crewalk, 2008, p. 4). The review also noted that these adverse reactions presented less risk than the risk of untreated hepatitis C. The revised label included warnings about the impact of pediatric use on growth of the child.

Studies support different dosing calculation
Nevirapine (Viramune), which was first approved in 1996, was approved in 1998 for treatment of HIV infection in children ages 2 months of age to 16 years, with additional information submitted in 2002. The 2002 approval letter specified required studies to determine dosing for younger groups. The information submitted by the sponsor in 2007 provided for dosing down to age 15 days and also provided data to support calculation of pediatric dosing based on body surface area rather than weight (Belew, 2008b).

Risk-benefit assessment does not support pediatric use
Omalizumab (Xolair) was approved in 2003 for treatment of moderate to severe persistent asthma in individuals 12 years of age or older. Although this approval occurred during a period when pediatric study requirements were not in effect, FDA encouraged further pediatric studies and noted that pending legislation might require such studies (Risso, 2003). The sponsor submitted studies for the 6-to-11 age group in 2008. After the data were reviewed by FDA staff and considered in a meeting of the joint Pulmonary-Allergy, Pediatric, and Drug Safety and Risk Management Advisory Committee, the product's labeling was revised to include the statement "Considering the risk of anaphylaxis and malignancy seen in Xolair-treated patients ≥12 years old and the modest efficacy of Xolair in the pivotal pediatric study, the risk-benefit assessment does not support the use of Xolair in patients 6 to <12 years of age" (Starke, 2009; Genentech, 2010b).

STUDY ORIGINS AND OVERVIEW

Charge to the Committee

In late 2009, FDA approached the IOM about an examination of pediatric studies of drugs and biologics conducted under the provisions of BPCA and PREA (and their predecessor policies). This examination was called for in the 2007 reauthorizations of these policies as part of as part of the Food and Drug Administration Amendments Act of 2007 (FDAAA; PL 110-85). While planning was under way, Congress passed the Patient Protection and Affordable Care Act (PL 111-148) in March 2010, which included the Biologics Price Competition and Innovation Act. That legislation changed the specifications for biologic products, and the FDA altered the Statement of Task accordingly. The tasks for the study committee appointed by the IOM were:

1. Review and assess a representative sample of written requests issued by the Secretary [of the U.S. Department of Health and Human Services] and studies conducted under BPCA since 1997 and labeling changes made as a result of such studies.
2. Review and assess a representative sample of studies conducted since 1997 under PREA or precursor regulations, and labeling changes made as a result of such studies.
3. Using a representative sample of written requests issued by the Secretary and studies conducted under BPCA since 1997 and studies conducted since 1997 under PREA or precursor regulations, review and assess (a) the use of extrapolation for pediatric subpopulations; (b) the use of alternative endpoints for pediatric populations; (c) neonatal assessment tools; and (d) ethical issues in pediatric clinical trials.
4. Using a representative sample of studies conducted since 1997 under PREA or precursor regulations, review and assess the number and type of pediatric adverse events.
5. Review and assess the number and importance of biological products for children that are being tested as a result of the amendments made by the Biologics Price Competition and Innovation Act of 2009 [passed in 2010] and the importance for children, health care providers, parents, and others of labeling changes made as a result of such testing.
6. Review and assess the number, importance, and prioritization of any biological products that are not being tested for pediatric use.
7. Offer recommendations for ensuring pediatric testing of biological products, including consideration of any incentives, such as those provided under section 505A of the Federal Food, Drug, and Cosmetic Act or section 351(m) of the Public Health Service Act.

Unlike many other IOM committees, this committee was not asked to make recommendations except with respect to recently enacted policies to provide incentives for pediatric studies of biologics. This report does, however, include conclusions and suggestions or options for consideration by Congress and FDA. The report is written for a diverse audience, including not only policy makers but also companies that develop pharmaceutical and biologic products subject to the incentives and requirements of

BPCA and PREA, researchers who study drugs and biologics in pediatric populations, professional societies and child health advocacy groups that promote pediatric research, and others interested in better information to guide clinical care for children.

For the most part, the committee examined studies intended to support initial labeling of a drug or biologic for use in pediatric age groups as approved by FDA. It did not investigate policies and activities to monitor the safety and effectiveness of products after they have been approved for pediatric use. The committee did, however, consult the postapproval (1-year) safety reviews that FDA's Pediatric Advisory Committee is required to conduct following a labeling change under BPCA or PREA. Such monitoring is important because the use of approved products in real-world clinical practice may reveal safety problems or shortfalls in effectiveness that are not evident in the relatively short-term controlled studies that FDA typically requires to support product approvals.

The absence of information about pediatric use or pediatric studies in the labeling of a medication does not mean that there have been no well-controlled studies of a drug's safety or efficacy. The committee could not, however, systematically evaluate either the extent of off-label use of medications with children or the extent to which there are controlled studies (other than those reflected in product labeling) to support or contradict such use for specific drugs and indications.

FDA did not ask the IOM to assess the impact of BPCA and PREA on clinical practice or child health, for example, the extent to which off-label use of a product decreased following labeling changes that described studies with negative safety or efficacy findings. The study committee recognizes that clinical practice is not always consistent with scientific evidence and also that many factors such as nutrition and environmental hazards affect the health and well-being of children.

Overview of Conclusions

In the course of its work, the committee reached several conclusions that are discussed in later chapters. Summarized, the conclusions are as follows:

- *Pediatric studies conducted under BPCA and PREA are yielding important information to guide clinical care for children.* The yield varies by medical condition, type of product, and age group. The information from pediatric studies sometimes supports and sometimes challenges expectations and assumptions about the efficacy, safety, and pharmacokinetics of drugs in children of different ages. The timely conduct of studies with children can discourage potentially unsafe off-label use of drugs approved for adults and encourage the timely incorporation of safe and effective drugs into pediatric care.
- *Some studies requested under BPCA or required under PREA do not achieve their full potential.* Reasons vary and may include the inability of sponsors to recruit sufficient numbers of children, the use of weak study designs and underpowered samples, the lack of dose-ranging studies to guide efficacy trials, and the omission of relevant study information from product labeling. More careful specification of requested and required studies combined with advances in the science of clinical trials would increase

the likelihood that studies will provide uniformly high-quality information for clinicians who care for children.

- *More timely planning, initiation, and completion of pediatric studies would benefit children*. European requirements for the submission of plans for pediatric studies apply somewhat early in the drug development process, whereas U.S. requirements apply later than is needed for access to credible safety and efficacy data for adults that are sufficient to support the planning and initiation of pediatric studies. Delayed in sponsor completion of some studies required under PREA is also a concern.
- *Pediatric drug studies remain particularly limited in certain areas, including the use of medications with neonates and the long-term safety and effectiveness of medications used for all pediatric age groups.* The lack of information about the long-term safety of drugs is a general concern, but it is a special worry for developing children. Questions about long-term safety exist both for drugs that may be used for decades for chronic conditions and for drugs for which relatively short-term use may have adverse consequences on a child's development months or years later. Many drugs commonly used to treat premature and sick neonates are older drugs that have not been adequately evaluated in studies with this vulnerable age group.
- *Congress has significantly expanded professional and public access to information from pediatric studies conducted under BPCA and PREA and has thereby enhanced the value of these studies.* Although the addition of information to product labeling is important, other valuable information is included in FDA clinical and clinical pharmacology reviews of the pediatric studies submitted to support a labeling change. Access to such information from studies associated with labeling changes prior to September 2007 remains limited, especially for studies conducted under PREA.
- *The reauthorization processes for BPCA and PREA have improved the policies in both acts, but the short term of reauthorizations creates uncertainties for industry and for FDA.* Since 1997, Congress has strengthened the application of expertise in pediatrics to the development of requests and requirements for pediatric studies and to the review of submitted studies. It has directed the inclusion of information from pediatric studies in product labeling in most cases and required a follow-up assessment of safety information from the first year following a pediatric labeling change. At the same time, frequent reauthorizations of the policies—every 5 years—create uncertainties for sponsors, given the long lead time for planning, conducting, analyzing, and submitting studies, and they may discourage FDA from developing final and updated guidance on BPCA and PREA.
- *Pediatric studies of biologics conducted under PREA have generated valuable information. The 2010 expansion of BPCA to cover biologics has potential to expand knowledge further, but it is too early to assess its effects.* Almost 90 percent of biologics investigated by the committee have been the subject of some study with children. Of the dozen biologics that have not been studied with children, most were approved for indications that are not diagnosed or very rarely diagnosed in children. Given the applicability to biologics of long-standing policies such as the 1984 Orphan Drug Act and PREA and the broad range of existing pediatric research on biologics, BPCA may have a valuable but more modest effect in encouraging studies of biologics than was the case for small-molecule drugs.

Report Structure

This rest of this chapter provides some historical context and defines key terms. In this and subsequent chapters, unless otherwise indicated, references to studies conducted under BPCA and PREA also encompass studies undertaken as result of the preceding policies (e.g., the Pediatric Rule) that are described below. Chapter 2 briefly reviews how children's development affects their response to drugs and discusses ways in which pediatric drug research must take children's growth and development into account. Chapter 3 describes key features of BPCA and PREA in the broader context of U.S. regulatory policies to ensure drug safety and efficacy. Public policy is also the focus of Chapter 4, which discusses policies for the protection of human research participants, including special protections for children. This chapter also describes some of the ethical issues that the committee encountered in its assessments of studies conducted under BPCA and PREA (Task 3d).

Chapter 5 examines elements of safety and efficacy determinations in studies conducted under BPCA and PREA. It considers FDA conclusions about the safety profile of a drug or biologic based on judgments about the source and importance of adverse events reported by study sponsors (Task 4). It also considers the use of alternative endpoints and extrapolation in determinations about efficacy (Tasks 3a and 3b). Chapter 6 discusses the complexities of assessing the safety and efficacy of drugs in neonates and describes the relatively small number of BPCA- and PREA-related labeling changes for this age group (Task 3c). Chapter 7 builds on the preceding chapters to consider the value of studies requested or required under BPCA and PREA and the value of the information added (or not added) to product labeling as a result of these studies (Tasks 1 and 2). Chapter 8 looks at incentives and requirements for pediatric studies of biologics and identifies and discusses the small number of biologics that have not been evaluated in studies with children (Tasks 5, 6, and 7).

Appendix A describes committee activities and explains the methods the committee used to select the representative sample referred to in the Statement of Task. Appendix B discusses the dissemination of information from FDA-approved drug labeling to professionals through various intermediary resources. Appendix C presents additional information about the use of biologics in pediatric populations, and Appendix D summarizes data on pediatric labeling and pediatric studies of biologics that FDA has approved since 1997. Appendix E summarizes changes in the specifications of written requests for pediatric studies of drugs for hypertension, and Appendix F provides brief biographies of committee members and project staff.

EVOLUTION OF POLICIES TO PROMOTE PEDIATRIC STUDIES OF DRUGS AND BIOLOGICS

Harm to Children as a Spur to Regulation of Drug Safety and Efficacy

FDA, the agency responsible for administering BPCA and PREA, owes its existence and modern responsibilities, in some measure, to public reaction to the injuries,

illnesses, and deaths of children that were caused by unsafe and unregulated medical products. For example, the federal regulation of vaccines and other biologics dates to the Biologics Control Act of 1902 (PL 57-244), a year after more than a dozen children died from tainted diphtheria antitoxin and other children died from contaminated smallpox vaccine (Junod, 2002). The law assigned responsibility for regulation of vaccines and antitoxins to the Hygenic Laboratory (which eventually became the National Institutes of Health [NIH]) (NIH, 2011b). Four years later, in 1906, Congress passed the Pure Food and Drugs Act (PL 59-384). It set certain standards for the labeling and lawful interstate transport of drugs and created the foundation for what later became the FDA. Although drugs could be removed from the market under the law, the law did not require drug testing or government approval.

The deaths in 1937 of more than 30 children from a product called Elixir Sulfanilamide contributed to the passage of the Food, Drug, and Cosmetic (FDC) Act of 1938 (PL 75-540). Ironically, the development of this deadly product resulted from the manufacturer's effort to create a form of the drug—an early antimicrobial—that was suitable for young children and others who could not swallow pills (Ballentine, 1981; Wax, 1995). The formulation, which was tested for palatability and appearance but not safety, unfortunately included diethylene glycol, a toxic substance found in antifreeze. Among other provisions, the FDC Act required the approval of new drugs prior to marketing on the basis of evidence of safety and also required that drug labels include information on how to use the products safely. It did not require evidence of efficacy.

Further legislation came after women who took the drug thalidomide in the 1950s and early 1960s gave birth to thousands of children with limb and other deformities. An FDA medical officer is credited with keeping the drug off the market in the United States, and the tragedy itself is credited with mobilizing support for passage of the Kefauver-Harris Amendments to the FDC Act (PL 87-781) (Kuehn, 2010). These 1962 amendments required that FDA approval of drugs be based on evidence not only of safety but also of efficacy as demonstrated in well-controlled clinical trials.

Yet another tragedy—deaths and permanent paralysis linked to a contaminated polio vaccine—prompted a strengthening of the oversight of biologics and the creation in 1955 of an independent Division of Biologics Control in the National Institutes of Health (FDA, 2002). In 1972, responsibility for regulation of biologics was transferred to a new Bureau of Biologics (now the Center for Biologics Evaluation and Research) at FDA.

Following the 1962 amendments to the FDC Act, FDA commissioned the National Research Council (NRC) of the National Academy of Sciences to review the effectiveness of drugs approved between 1938 and 1962 as a basis for later regulatory consideration (NRC, 1969; see also NAS, undated; IOM, 1992). Based on the work of more than 180 experts in 30 panels, the NRC report concluded that only 12 percent of drugs were effective for all their claimed uses and 60 percent were not effective for at least one claimed use (Hecht, 1984). As described by FDA, the report found overall that "the quality of the evidence of efficacy, as well as the quality of the labeling claims, is poor" (21 CFR 201.200).[2]

[2] Subsequently, under the title Drug Safety and Efficacy Implementation (DESI), FDA created a process for acting on the NRC study results for previously approved drugs that continues. As recently as 2011, FDA cited the DESI process in announcing plans to take action against "unapproved and misbranded" prescription products "offered for relief of symptoms of cold, cough, or allergy" (76 FR 11794).

Policies to Promote Pediatric Research Adopted Before 1997

Although the 1938 FDC Act provided the first requirements that drugs be found safe and the 1962 legislation required demonstration of efficacy, that regulatory framework did little to ensure that safety and efficacy studies would, in fact, extend to children for whom FDA-approved drugs were being prescribed off-label but legally. Drugs or elements of drugs that prove safe for adults may harm children. For example, in 1982, 16 premature infants died from respiratory distress linked to intravenous solutions and diluted medications containing excessive amounts of benzyl alcohol, a preservative (Gershanik et al., 1982). Unlike diethylene glycol, which is toxic to adults as well as children, the use of benzyl alcohol was not unsafe for adults and had not raised warning signs for use by older children.

The 1970s saw growing recognition of the need for pediatric drug studies as well for formal protections for both child and adult participants in biomedical research. In 1974, the American Academy of Pediatrics (AAP) issued a report, developed under contract with FDA, titled *General Guidelines for the Evaluation of Drugs to Be Approved for Use During Pregnancy and for Treatment of Infants and Children* (AAP, 1974; see also FDA, 1977). In 1977, the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research produced a report and recommendations on the ethics of research with children (National Commission, 1977). Citing the Commission's final report (commonly referred to as the Belmont Report) and its endorsement of justice in the distribution of research benefits and burdens, FDA argued two decades later that the "exclusion of pediatric patients from [drug] clinical trials may deny them an equitable share of the benefits of research" (62 FR 43900, 43908). It made this argument in support of the Pediatric Rule (FDA, 1997).

One of the first policies aimed directly at improving pediatric prescribing information came in 1979, when FDA issued regulations requiring that the precautions section of drug labeling include a subsection on pediatric use (44 FR 37434; see also 71 FR 3922 and 21 CFR 201.57(f)(9)). In addition, if the drug was not approved for use by children, the labeling had to state that safety and effectiveness in children (or a subgroup of children) had not been established. If the drug had been approved for pediatric use, the label had to specify the approved indication and provide information on dosing and administration. The regulation did not require the development of pediatric data for labeling.

Fifteen years later, in 1994, FDA issued new regulations revising specifications for the pediatric use section of drug labeling (59 FR 64240). The Pediatric Labeling Rule required drug manufacturers to review existing literature and other data to determine whether the drug label needed to be modified, through an application to FDA, to add pediatric information. These applications were requested by December 13, 1996.

The commentary on the 1994 regulations noted that, contrary to the impression of some, the law did not always require that pediatric labeling be based on well-controlled clinical trials. FDA could waive the requirement if other sources of information would suffice. Specifically,

> [a] pediatric use statement may also be based on adequate and well-controlled studies in adults, provided that the agency concludes that the course of the disease and the drug's effects are sufficiently similar in the pediatric and adult populations to permit extrapolation from the adult efficacy data to pediatric patients. Where needed, pharmacokinetic data to allow determination of an appropriate pediatric dosage, and additional pediatric safety information must also be submitted. (62 FR 43900; see 21 CFR 201.57 (f)(9)(iv))[3]

The use of extrapolation is discussed further in Chapter 5.

To support companies studying drugs in children, FDA created a working group on pediatric formulations in 1995 to examine chemistry and manufacturing issues in the development of new formulations (NICHD, 2006). NIH also created a pediatrics formulation initiative as a part of its work on BPCA, which is described later in this chapter.

After a few years, FDA concluded that the 1994 regulations had done little to increase pediatric information on drug labels. Specifically, "[o]ver a 6-year period between 1991 and 1996, drug sponsors promised to complete 71 postmarketing pediatric studies. Only 11 were completed" (FDA, 2001a, p. 8). In 1998, to justify new regulations, the agency made this case:

> The response to the 1994 rule has not substantially addressed the lack of adequate pediatric use information for marketed drugs and biological products. Pediatric labeling supplements were submitted for approximately 430 drugs and biologics, a small fraction of the thousands of prescription drug and biological products on the market. Of the supplements submitted, approximately 75 percent did not significantly improve pediatric use information. *Over half of the total supplements submitted simply requested the addition of the statement "Safety and effectiveness in pediatric patients have not been established."* (63 FR 66631) (emphasis added)

Policies to Promote Pediatric Drug Research, 1997 to 2010

The response to the limited effects of previous efforts to encourage pediatric drug studies and increase pediatric drug labeling was twofold. One route involved the creation through legislation of incentives for drug studies; the other relied on requirements for studies established by regulation. The discussion below briefly summarizes the policies; Chapter 3 provides more details.

[3] In November 1996, the agency sent letters to 250 manufacturers asking if and when they intended to file applications; by December 30, it had received 40 responses. In addition, it received a request from the Pharmaceutical Research and Manufacturers of America that the compliance date be extended because "some companies with large numbers of products had encountered unexpected problems in gathering the required information" (61 FR 68623).

Incentives for Pediatric Studies and Pediatric Exclusivity: FDAMA and BPCA

Among many other provisions, FDAMA provided companies with market protections—pediatric exclusivity—when they undertook pediatric studies of a drug in response to formal written requests from FDA. As passed in 1997, the relevant section of the law was not entitled "Best Pharmaceuticals for Children," although it incorporated proposed legislation that had been first introduced in 1992 under the title "Better Pharmaceuticals for Children" (AAP, 2008).

Pediatric exclusivity extends for 6 months beyond any existing period of exclusivity and patent protection, which means that products that have no remaining patent life or exclusivity are usually not eligible for the exclusivity incentive. Exclusivity applies to all forms of a company's drug that contain the same active moiety (in essence, the active ingredient in the drug). For a drug with a lucrative market in adults, this incentive can be significant, producing net economic returns in the hundreds of millions of dollars (see, e.g., Li et al., 2007 and Baker-Smith et al., 2008).

Congress reauthorized the exclusivity provisions of the 1997 legislation in BPCA of 2002 (PL 107-109) and again in 2007 as part of FDAAA. BPCA is once again up for reauthorization by October 1, 2012.

FDA issued guidance for industry on pediatric exclusivity in 1998 and subsequently revised the guidance in 1999 (CDER/CBER, 1999). That guidance has not been updated or reissued to reflect subsequent legislative changes in 2002 and 2003. For companies considering or planning studies under BPCA, FDA will advise about current requirements and expectations.

Requirements for Pediatric Studies

The same year that Congress created the pediatric exclusivity incentive for pediatric drug studies, FDA on its own initiative proposed regulations—the Pediatric Rule—that required companies to undertake pediatric studies of drugs and biologics under certain conditions. It issued the revised, final regulations in 1998 with an effective date of April 1, 1999 (63 FR 66631; 21 CFR 314.55(a) and 601.27(a)). Except when FDA waived or deferred its application, the rule required that the submission of a drug or biologics marketing application contain a pediatric assessment if the submissions involved a new active ingredient, indication, drug form, dosing regimen, or route of administration. The FDA issued draft guidance on the application of the Pediatric Rule in November 2000 (FDA, 2000).

In December 2000, groups opposing the regulations filed suit claiming that FDA exceeded its authority in issuing them. In 2002, a U.S. district court agreed and enjoined their enforcement (*Association of Am. Physicians & Surgeons, Inc. v. FDA*, 226 F. Supp. 2d 204 (DDC 2002)). Supporters of the regulations went to Congress, which codified the key features of the Pediatric Rule in the PREA of 2003 (PL 108-155). In 2005, FDA published draft guidance for industry on compliance with PREA (70 FR 53233). That guidance has not been updated or made final.

Like BPCA, PREA was reauthorized in 2007 as part of FDAAA. It, too, is due for reauthorization by October 1, 2012.

PREA Compared with and in Conjunction with BPCA

Following the precedent of the Pediatric Rule, PREA applies not only to drugs but also to biologics and, under certain circumstances, to generic products. The incentives established by BPCA did not extend to biologics until the passage of the Patient Protection and Affordable Care Act of 2010 (see Chapter 8). Under PREA, FDA can require pediatric studies only for the indications specified in an application for FDA approval, whereas requests under BPCA can cover studies for other indications, including indications that were approved before the adoption of either policy. Drugs with designation under the Orphan Drug Act are exempt under PREA but can be the subject of written requests.

The incentives of BPCA and the requirements for PREA can operate in tandem for the same product and sponsor. That is, FDA can require pediatric studies and also request them to give an incentive for the companies to conduct the required studies in a timely fashion. Congress has made the BPCA and PREA more consistent in certain respects over the years, particularly with respect to public access to information developed through requested or required pediatric studies.

As described further in Chapter 5, from July 1998 through October 2011, FDA approved more than 425 labeling changes associated with studies requested under BPCA or required under PREA. More than 380 of these changes involved the submission of information from new pediatric studies. During the same time period, FDA

- issued more than 330 written requests under BPCA, nearly half of them in the first 2 years of the program;
- approved 145 labeling changes related solely to such requests and granted exclusivity to 174 active moieties;
- approved at least 179 labeling changes related solely to PREA requirements;
- approved 49 labeling changes related to both BPCA requests and PREA requirements; and
- made public clinical and other reviews associated with 139 labeling changes (since September 2007).

Other Activities and Policies at FDA

FDA supports other policies and initiatives not directly related to BPCA or PREA that may encourage the study of drugs in children. As discussed in Chapter 8, the Orphan Drug Act has promoted the study and approval of drugs for rare diseases, many of which affect children. Products with orphan drug designations are exempt from PREA requirements, but many orphan drugs are approved for pediatric use.

In addition, through its initiative on unapproved drugs, the agency has sought to get sponsors of such drugs, generally older products, to provide information sufficient to

support their approval, including for use by relevant pediatric populations (FDA, 2006a). After announcing in 2007 that sponsors of three previously unapproved pancreatic enzyme products had until April 2010 to secure agency approval, FDA approved the three products by that date (FDA, 2010d). All are labeled for the treatment of exocrine pancreatic insufficiency due to cystic fibrosis or other conditions in all pediatric age groups.

National Institutes of Health

NIH supports pediatric clinical research on a wide range of specific diseases and conditions and likewise funds basic research in many areas that may eventually translate into products that benefit children. In 1998, in response to congressional directives, NIH issued policies and guidelines to increase the participation of children in agency-funded research. The goal is "that adequate data will be developed to support the treatment modalities for disorders and conditions that affect adults and may also affect children" (NIH, 1998, unpaged). As described in Chapter 2, NIH has recently announced an initiative to investigate new strategies for creating and testing drug formulations suitable for children.

In addition, because pediatric exclusivity is generally not relevant to drugs that have no existing exclusivity or remaining patent life, Congress, as part of BPCA of 2002, directed NIH to create a pediatric drug development program and to set priorities for pediatric studies of off-patent drugs. (The priority-setting process now extends to pediatric therapeutics more broadly.) Under certain circumstances, FDA may also refer to NIH a written request for studies of an on-patent drug if the sponsor has declined the request and the agency determines that the requested information is still needed. (See Chapters 3, 6, and 7 for further discussion of the role of NIH under BPCA.)

International Activities and Policies

Pharmaceutical research is global. Many pediatric studies conducted under BPCA or PREA include foreign study sites, and some (e.g., those for prevention of HIV transmission from mother to child) may be undertaken entirely outside the United States. These activities are subject to the laws and regulations of many countries.

FDA is involved in a number of efforts to harmonize national policies and otherwise try to limit some of the problems caused by different policies. These efforts include frequent communication with agency counterparts in the European Medicines Agency, which has somewhat different policies to require or encourage pediatric drug studies. Oversimplified, a key difference is that European policies require the submission of a pediatric study plan earlier in the process of drug development. Other differences in these policies—and efforts to harmonize policies—are briefly described in Chapter 3. Chapter 4 discusses ethical aspects of studies conducted outside the United States.

In addition, the World Health Organization (WHO), which also provides guidance and encourages consensus on national regulation of medications, has the Make Medicines Child Size initiative that includes working in partnerships with governments, researchers, industry, and others to promote the development of medicines for children (WHO,

2011b). As part of a broader program to identify drugs to meet priority health needs of the majority of the world's population, WHO has also developed a list of what it describes as essential medicines for children (WHO, 2011a).

SELECTED DEFINITIONS

This section discusses a number of terms used in the committee's Statement of Task and defines several other key terms used in the report. The terms *drug*, *biologic*, and *active moiety* are defined in Chapter 3. Additional terms are defined in later chapters.

Pediatric Age Group, Children

Neither BPCA nor PREA defines the age range covered by the term *pediatric population* or *pediatric age group*. Federal regulations on drug labeling define the pediatric population as the age group from "birth to 16 years, including age groups often called neonates, infants, children, and adolescents" (21 CFR 201.57(f)(9)). Elsewhere, FDA has described the age ranges for pediatric subpopulations as follows: "neonate—birth to up to one month; infant—one month up to 2 years of age; child—2 years up to 12 years; and adolescent—12 years up to 16 years" (see, e.g., FDA, 1996).[4] It is not always clear when a particular FDA document refers, for example, to the "12- to 16- year" age group whether it is referring to children from the ages of 6 years up to but not including 12 years or to children from the ages of 6 years to 12 years inclusive.

In practice, when it specifies the age groups for which pediatric studies may be requested or required, FDA is not tied to fixed age categories. It typically relies on knowledge of the drug and condition to be studied as the basis for age ranges and often specifies ranges that differ from those described above. When specifying studies for the youngest age groups, FDA may distinguish between term and preterm infants and may consider gestational age (usually calculated as the number of weeks from the start date of the mother's last menstrual period). Among older children, FDA sometimes defines a study population based on extent of pubertal development. In general discussions, this report uses the terms *pediatric population* and *children* interchangeably.

Pediatric Studies, Clinical Studies

As defined in BPCA, the term *pediatric studies* refers to clinical investigations with pediatric age groups in which use of a drug is anticipated (21 USC §355a(1)). The term is most clearly applied to studies that include only pediatric populations. However,

[4] In contrast, FDA guidance on pediatric studies of medical devices (which are not covered by PREA and BPCA) includes as adolescents individuals "up to the age of 21" (CDRH, 2004, p. 4). Other federal agencies may also use different definitions. For example, in infant mortality and other statistics, the Centers for Disease Control and Prevention define infancy as the period from birth up to 1 year of age. To cite a different example, under NIH policies, an 18-year-old might be an adult for purposes of consenting to participation in research but a child under a policy on the inclusion of children (up to age 21 years) in research (NIH, 1998).

studies submitted in support of labeling for a pediatric age group occasionally include children in a larger study group that includes adults. For example, when omalizumab (Xolair) was originally approved in 2003 for use in patients ages 12 years and older, the critical clinical efficacy studies included participants ages 12 to 74 years in one trial and 12 to 76 years in the other (Kaiser, 2003). (Adolescents comprised approximately 6.5 percent of participants in one trial and approximately 8 percent in the other.)

Sponsor submissions to FDA are not public. Thus, when this report refers to *assessments of studies*, it means assessments of studies as they are described in FDA staff reviews, primarily the clinical, clinical pharmacology, and statistical reviews.

For the initial approval of a new drug or biologic, FDA typically requires an extensive range of preclinical and clinical studies. The assessments in this report focus on *clinical studies* or *trials*, that is, studies with humans. FDA recently made a distinction between studies and trials as follows: "*Clinical trials* are any prospective investigations in which the applicant or investigator determines the method of assigning the drug product(s) or other interventions to one or more human subjects. *Studies* are all other investigations, such as investigations with humans that are not clinical trials as defined above (e.g., observational epidemiologic studies), animal studies, and laboratory experiments" (CDER/CBER, 2011). In this report, a *trial* is one type of clinical study.

When FDA defers the submission of pediatric studies that are required under PREA to a later date because the product is ready for approval for adults (see Chapter 3), these studies are referred to as *postmarket study commitments*. Although they are postmarket studies in the sense that they occur after a drug have been approved for marketing for use by adults (or another pediatric age group), the pediatric studies submitted at a later date will usually include one or more Phase I, II, or III trials (see Box 1-2). Thus, this report does not refer to pediatric studies requested under BPCA or required under PREA as Phase IV trials.

BOX 1-2
Types of Clinical Trials

Phase I trials initiate the study of candidate drugs and biologics in humans. Such trials typically assess the safety and tolerability of a drug, routes of administration and safe dose ranges, and the way in which the body processes the drug (e.g., how it is absorbed, distributed, metabolized, and excreted). They usually involve less than 100 individuals, often healthy volunteers (in adult trials).

Phase II trials continue the assessment of a drug's safety and dosing but also begin to test efficacy in people with the target disease, including children. These studies may include a range of controls for potential bias, including use of a control group that receives standard treatment or a placebo, the random assignment of research participants to the experimental and control groups, and the concealment (blinding) from participants and researchers of a participant's assignment. The studies may involve hundreds of participants, although pediatric trials are usually smaller.

Phase III trials are expanded, usually well-controlled investigations of safety and efficacy that are intended to allow a fuller assessment of a drug's benefits and harms and to provide information sufficient to prepare labeling or instructions for the use of the drug. These studies may involve hundreds to thousands of research participants and multiple sites.

Phase IV studies occur after a new product or a new indication, drug form, dosing regimen, or similar change is approved for marketing. They are highly variable in their designs and purposes. Scientifically focused studies are typically intended to provide further information about outcomes in clinical practice, for example, when the drug is used over periods longer than those studied in the trials used to support FDA approval.

SOURCES: Adapted from FDA (2010a) and IOM (2010).

Benefit, Harm, Risk

The public health goal of drug development is to create drugs that produce desired health benefits and avoid or minimize harm insofar as possible. A *benefit* is a valued and helpful outcome from an intervention; a *harm* is an unwanted and hurtful outcome.

Risk refers to the potential for harm. Few medical interventions are without risks. The challenge for those evaluating studies submitted in support of a drug's approval is to weigh the projected benefits against the risks.

Adverse Event, Safety Signal, Efficacy, Effectiveness

In the context of clinical studies being undertaken to support the approval of a drug or biologic, an *adverse experience* (*adverse event* is used in this report) is defined in federal regulations as "any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related" (21 CFR 312.32(a)). The regulations use the term *adverse reaction* to describe an adverse event caused by a drug. In addition to lengthy descriptions and analyses of adverse events, FDA reviewers usually provide an overall assessment of a product's *safety profile*, specifically, whether the profile was similar to or different from that found in adults (unless the product has not been evaluated in adults) and whether it identified serious drug-related adverse events.

Efficacy refers to the achievement of desired results in controlled clinical studies. *Effectiveness* refers to the achievement of desired results in actual clinical practice. Results in clinical practice may differ significantly from results in carefully controlled clinical trials. Although the FDC Act uses the term effectiveness to describe positive results reported in clinical trials (21 USC 355), FDA clinical reviews and other documents use the term efficacy rather than effectiveness in discussing such data.

Alternative Endpoint, Extrapolation

This report uses the term *alternative endpoint* to refer to a measure of efficacy in a pediatric clinical trial that takes pediatric development into account and thus differ from endpoints for adult studies for the condition being investigated. For example, in studies with adults, investigators may rely on self-reports of symptoms, whereas in studies with children, particularly young children, they may rely on reports from parents or on

investigator assessments based on such physical expressions as crying or grimacing or behaviors such as loss of appetite. For conditions that are found solely or primarily in children, the pediatric endpoint may be unique.

In the context of pediatric studies conducted under BPCA or PREA, *extrapolation* refers to FDA's acceptance of clinical trial and other information developed in studies with adults to support decisions about the approval of a product for pediatric use. As discussed in Chapters 3 and 5, FDA also may accept extrapolation of data from one pediatric age group to another.

Label, Labeling

Under the FDC Act, the drug *label* refers to "written, printed, or graphic matter upon the immediate container of any article," whereas the term *labeling* refers to "all labels and other written, printed, or graphic matters" accompanying a product (whether affixed or not) (21 USC 321(k) and (m)). The former term is popularly applied to the short label affixed to prescription drug containers.

Consistent with FDA usage, this report uses the term *labeling* to refer to the longer and more detailed prescribing information (sometimes called *package inserts*) that FDA approves to accompany prescription drugs. Also, because labeling changes require FDA authorization, this report sometimes uses the terms *labeling change* and *approval* interchangeably, including when a product is approved for the first time and thus has no previous labeling to change.

As a shorthand expression, this report may use the term *pediatric labeling* to describe a product that is explicitly labeled for use by all or some pediatric age groups. Many products do not have pediatric labeling but do have some information in the labeling from pediatric studies, for example, brief reports of clinical trials that did not show safety and efficacy.

Indications, On-Label Use, Off-Label Use

FDA approves drugs and biologics for specific indications. An *indication* describes a particular use of a product, for example, for acute treatment of schizophrenia or long-term control of asthma symptoms. FDA may approve use of a drug for an indication for a medically relevant subset of people with a condition, for example, those with severe disease or those with disease that is not responsive to commonly used or less risky treatments. Labels, particularly labels that have not recently been updated, are not always explicit about the age groups to which the approved indication applies.

On-label use refers to clinical use that is covered by a product's labeling, primarily the indication(s) and age group(s) described in the label. Physicians may legally use drugs *off-label* for uses that are not approved and included in a product's labeling. Companies may not explicitly promote such uses.

Applicant, Sponsor, Company, Manufacturer

In FDA terminology, an *applicant* or *drug sponsor* is "the person or entity who assumes responsibility for the marketing of a new drug, including responsibility for compliance with applicable provisions of the Federal Food, Drug, and Cosmetic Act and related regulations" (FDA, 2010a). The sponsor of an application for FDA approval of a drug or biologic is typically a pharmaceutical or biotechnology company.

Rarely, applications come from public or nonprofit agencies. For example, the California Department of Health Services developed, tested, and received FDA approval for botulism immune globulin (BabyBIG) for the treatment of infant botulism (Arnon, 2007). Notwithstanding such examples, this report uses the terms *sponsor*, *applicant*, *company*, and *manufacturer* interchangeably.

As companies consider the planning and conduct of pediatric studies, they must consider the particular scientific, ethical, legal, practical, and economic aspects of such studies. The next chapter provides an overview of developmental pharmacology and adaptations in research strategies to accommodate the ways in which children of different ages differ from adults and each other.

2
Children's Growth and Development and Pediatric Drug Studies

As context for later discussions of ethics, safety, and efficacy in pediatric studies, this chapter provides an overview of how children's growth and development may affect their responses to medications. Medications that are generally safe and effective for adults may be unsafe or ineffective—or both—for some or all pediatric age groups or may require changes in dosing forms, calculations, or schedules to be safe and effective. This disparity underscores the necessity for pediatric drug studies. This chapter also discusses how differences between children and adults may require alterations in the design, conduct, and analysis of such studies.

As a prelude to the rather technical discussion of developmental pharmacology, the chapter begins with an example of the sometimes fatal consequences of the lack of drug studies with children, especially the youngest children. The case involves an antibiotic that was used to treat neonates before its safety had been documented in that age group.

THE CASE OF CHLORAMPHENICOL

Chloramphenicol was discovered in the late 1940s and found to be effective against many different infections caused by a wide range of organisms, from salmonella to rickettsia (Meissner and Smith, 1979). The pharmacokinetics of chloramphenicol in children were reported in 1951 (Kelly et al., 1951).

During the 1950s, as pediatricians made increasing use of the drug to treat a variety of infections, the American Academy of Pediatrics (AAP) Committee on Infectious Diseases offered dosing recommendations for the drug (Kempe, 1955). Most of the studies reviewed as a basis for the recommendations included children and infants (some as young as 1 month) but no newborns. Then, in response to the increasing survival rates for premature newborns, AAP sponsored a seminar in 1956 on a broad range of problems specific to premature and newborn infants. To reduce mortality from infections, some discussants recommended that premature newborns born after premature rupture of membranes (24 to 48 hours prior to delivery) be treated prophylactically with antibiotics, including chloramphenicol (Day and Silverman, 1957), even though no controlled studies had investigated the drug's safety and efficacy for use with neonates.

In 1959, a report of three newborns who died without explanation during treatment with chloramphenicol (Sutherland, 1959) was soon followed by the report of a randomized clinical trial to evaluate the effectiveness of prophylactic antibiotics in reducing mortality in premature newborns following prolonged premature rupture of membranes (Burns et al., 1959). In the trial, mortality rates for the two groups treated with chloramphenicol were 68 and 60 percent. In contrast, mortality rates for the placebo group and the group treated with different antibiotics (penicillin or streptomycin) were 19 and 18 percent, respectively.

Other studies determined that newborns, in particular, premature newborns, could not eliminate the drug from their bodies as fast as older infants and children (Weiss et al., 1960). As a result, dosing at levels used for older children and adults increased chloramphenicol concentrations to dangerous levels. This led to the "gray syndrome" (or "gray baby syndrome"), which was characterized by abdominal distension beginning 2 to 3 days after the start of chloramphenicol treatment and then by grunting respirations, cardiovascular collapse with gray skin color, and death. Although most off-label use of drugs does not have such dire consequences, the experience with chloramphenicol underscores the potential hazards of using new drugs in children, especially newborns, and the importance of controlled studies to guide decisions about when, how, and whether to use them.

DEVELOPMENTAL PHARMACOLOGY AND PHARMACOGENOMICS

Basic Aspects of Developmental Pharmacology[1]

The visible changes that occur as a newborn infant grows into a toddler, child, adolescent, and then a young adult are well known. As knowledge of the biology underlying this normal growth and development has increased, so has the recognition that these changes significantly affect the responses of growing children to medications. Such changes require evidence-based methods for selecting safe and effective doses of medications for children at different stages of development and for engineering appropriate delivery systems for these medications. Adjustments in dosing are often more complicated than simply scaling down the dose determined for adults on the basis of a child's age or weight.

The study of what happens to a drug in the body is a key focus of the field of clinical pharmacology. Developmental pharmacology studies the changes that take place in the clinical pharmacology of drugs as a child grows from birth to adolescence.

Once administered, drugs undergo biochemical changes that allow their absorption, distribution, metabolism, and removal from the body (collectively referred to as the *pharmacokinetics* of a drug). These biochemical changes—which may occur in the intestinal tract, liver, or other organs through the action of drug-metabolizing enzymes—may facilitate absorption or elimination. Some of these enzymes are not fully active at the time of birth, especially premature birth. An important group of enzymes involved in

[1] Resources for this discussion include the work of Kearns et al. (2003), Ward and Lugo (2005), and Rakhmanina and Van Den Anker (2009). The Food and Drug Administration provided draft guidance on the conduct of pediatric pharmacokinetic studies in 1998 (CDER/CBER, 1998a).

drug metabolism includes cytochrome P450 (CYP), which is primarily present in the liver. One specific CYP can often metabolize several drugs that belong to the same drug class and carry out similar actions in the body. Conversely, a specific drug may also be metabolized by several different CYPs.

After a drug is absorbed into the bloodstream, it can quickly move throughout the body. For drugs taken orally, absorption from the gastrointestinal tract occurs more rapidly for drugs that are small molecules (those with a molecular mass of less than 500 daltons), not ionized, and fat soluble. Ionization—and therefore absorption—of drugs varies with the pH in the gastrointestinal tract, which ranges from very acidic in the stomach to more alkaline in the small intestine. Absorption differs between premature and term infants, and stage of development may also affect absorption for other modes of administration (e.g., through the skin).

After a drug is moved or distributed throughout the body, its concentration in the blood generally decreases. The extent to which a drug is distributed throughout the body depends on a number of factors, including how readily it dissolves in water. For drugs that are water soluble, this lowering of the concentration by dilution in body water is particularly important in premature newborns, who have proportionately more body water than do adults and older children. Individual dosages of water-soluble drugs for premature newborns must often be increased to adjust for this increased body water so that the drugs reach an effective concentration in the bloodstream.

After enzymatic changes, many drugs are eliminated in the urine. Others continue to undergo further biochemical changes that allow the drug or metabolite to be excreted into the bile. The steps to change a drug molecule into a form that is more readily eliminated by the body often require the action of a number of enzymes. In developing children, the individual enzymes for drug metabolism and conjugation usually do not mature at the same rate, nor does the maturation of an individual enzyme occur at a constant rate. For newborns and young children, the dose of a drug is often adjusted to the child's body weight or body surface area to adjust not only for size but also for the maturation of enzymes that occurs with growth.

Studies have demonstrated, however, that neither body weight nor body surface area fits the maturation process exactly. At some stages during growth, especially from a few months to several years of age, the rate of increase in liver activity for some CYPs exceeds the rate of growth, so the dose of a drug per unit of body weight must be as high as twice that in an adult to keep the concentration in a therapeutic range. In contrast, for premature newborns, many CYP enzymes are underdeveloped, and the drug doses must be given at intervals much longer than those used for older children or adults.

Without knowledge of the rates of drug removal from the body, dosing in the wrong amount and at the wrong interval can cause drugs to accumulate in newborns and infants, sometimes to toxic or even lethal concentrations. The only way to determine the correct dose of medications is to test them in children at different stages of development. Otherwise, children can be harmed. A dose that is too high may be toxic. A dose that is too low may be ineffective.

Premature newborns are a special challenge in determination of the appropriate dosages of medications because of their unique physiology as well as the difficulty of studying drugs in this fragile population. In the neonate, the liver's capacity for drug metabolism is immature for many but not all drugs, and the kidney is similarly immature

in filtering drugs selectively into the urine. Given that neonates born as early as 24 weeks (or 4 months) prematurely now commonly survive, the challenge for developmental pharmacology has increased.

For some drugs (e.g., aminoglycoside antibiotics), changes in the rate of clearance or elimination of drugs from the body may correlate with both gestational age (the number of weeks since the mother's last menstrual period) and chronologic age (age after birth).[2] For other drugs (e.g., pantoprazole), clearance may correlate more closely with chronologic than gestational age (Ward et al., 2010). As a general rule, how a drug is removed from the body needs to be studied both in preterm newborns, that is, infants born at less than 34 weeks of gestation, and in newborns born from 34 weeks of gestation to term. Separate studies may be needed for the most immature newborns (those born at 24 to 28 weeks of gestation).

Different diseases may also influence renal and liver clearance of drugs in children in ways that require dosage adjustments. For example, infants with intestinal problems who are unable to eat and must be fed intravenously often develop cholestasis (impaired bile flow). This condition reduces bile acids in the small intestine, which in turn reduces the absorption of fat-soluble drugs and the excretion of conjugated drugs into the bile and requires adjustments to some drug doses. In contrast, drugs such as phenobarbital and rifampin increase the activity of many drug-metabolizing enzymes in the liver. Again, the only way to determine the appropriate adjustments is by study with relevant pediatric populations.

As children move from infancy through childhood and adolescence, their developmental maturity—as it affects responses to drugs—more closely approaches that of adults (Carr and Ensom, 2003). Adolescent development is, however, highly variable. The onset of puberty in children who are living in similar environments and have no medical conditions that could accelerate or delay puberty may vary by as much as 4 to 5 years (Parent et al., 2003). For that reason, some studies of drugs of older children and adolescents use a measure of pubertal development (Tanner staging) rather than age to specify the upper or lower developmental boundary for enrollment in a trial. Behavior can also be an issue, for example, when uncertainties about adolescent compliance with self-administered dosing regimens complicate interpretation of clinical response or study measurements.

A National Institutes of Health (NIH) working group on adolescent therapeutics has recommended more research on a number of topics, including how pubertal development and body weight affect drug distribution and metabolism (NICHD, 2010). The group noted, for example, the need for studies to understand risk factors and other aspects of weight gain in adolescents using antipsychotic and certain other medications. As cited in Chapter 5, the Food and Drug Administration's (FDA's) Pediatric Advisory Committee has recommended that information about the possible risk of pediatric weight gain be added to the labeling of these drugs. In addition, some have argued that dosing strategies for studies of drugs for major depression in children, particularly adolescents,

[2] *Postmenstrual age* may also be used to describe the age of a preterm infant. It is the infant's gestational age at birth plus his or her chronological age (AAP Committee on the Fetus and Newborn, 2004). For preterm infants, chronological age differs from *corrected age*. The latter, which is used for preterm infants below the age of 3, is determined by subtracting the number of weeks that an infant was born before 40 weeks of gestation from his or her chronological age.

have not consistently taken into account the results of pharmacokinetic studies (Findling et al., 2006). The concern about weight may apply to medications prescribed for younger children as well as adolescents.

Pharmacogenomics and Developmental Pharmacology

One area of challenge and opportunity for pediatric drug studies requested under the Best Pharmaceuticals for Children Act (BPCA) or required under the Pediatric Research Equity Act (PREA) involves pharmacogenomics (see, e.g., Cohen and Ness, 2009; Hudson, 2011; Neville et al., 2011). Pharmacogenomics is the study of how individual genetic variability affects the body's response to medications (SACGHS, 2008). As of October 2011, FDA had identified almost 100 drugs with labeling that included pharmacogenomic information (FDA, 2011c). The inclusion of pharmacogenomic information in labeling is most common for oncology and psychiatry drugs. To cite an example in psychiatry, the labeling for aripiprazole (Abilify) advises dosing adjustments for patients identified by cytochrome CYP2D6 genotype as poor metabolizers (BMS, 2011).

In some cases, the inclusion of pharmacogenomic information in labeling takes the form of a boxed ("black box") warning. For example, a boxed warning on the label of the drug abacavir sulfate (Ziagen) states that hypersensitivity reactions to the drug can be fatal and that "patients who carry the *HLA-B*5701* allele are at high risk for experiencing a hypersensitivity reaction" (GSK, 2010, p. 1). This drug is approved for treatment of HIV infection in patients 3 months of age or older, and testing for this allele is now an accepted element of the standard of care for HIV-infected children (Panel on Antiretroviral Therapy and Medical Management of HIV-Infected Children, 2011).

Advances in pharmacogenomics may affect other drug therapies for children. To cite examples, two common childhood conditions—attention deficit hyperactivity disorder (ADHD) and asthma—have known genetic components that affect responses to certain drugs. In children with ADHD, the response to methylphenidate (which is found in drugs such as Ritalin and Concerta) is affected by polymorphisms in the dopamine transporter gene (*DAT1*) (see, e.g., Gruber et al., 2009). In the treatment of asthma, bronchodilation or the worsening of asthma in patients on continuous short-acting and long-acting beta-agonists is associated with polymorphisms in the β_2-adrenergic receptor gene (*ADRB2*) (see, e.g., Lima et al., 2009). In patients using inhaled corticosteroids, other genetic variations contribute to variability in airway responsiveness, lung function response, and clinical exacerbations. As in other areas, the developmental variability described in the first part of this chapter adds complexity and may limit the generalization to children of findings from pharmacogenomic studies with adults. For example, researchers recently reported that a pharmacogenetics-based dosing algorithm for warfarin that was derived from adult data consistently over-estimated the pediatric dose of the drug (Biss et al., 2011).

In addition to affecting treatment decisions, pharmacogenomics can aid the design of pediatric drug trials and other studies. Genotypic data can be included as a covariate in population-based analyses of pharmacokinetic or pharmacodynamic data, in which the contribution of the genotype to outcome can be examined (Neville et al., 2011). In

addition, genotypic information can be useful in identifying the reason for outlier pharmacokinetic or pharmacodynamic data in a given cohort of research participants, which may in turn allow a fuller understanding of variability in drug action. Incorporation of pharmacogenomics in clinical trial designs to better identify patient characteristics associated with differences in drug response could reduce the number of pediatric trials that fail to show efficacy because of a lack of sufficient information on such characteristics. Incorporation of pharmacogenomics could likewise allow reductions in sample sizes, which is a particular issue in pediatric studies.

These and other applications of pharmacogenomics have ethical implications that are beyond the scope of this brief discussion (see, e.g., Issa, 2002; Freuend and Clayton, 2003; Moran et al., 2011). Nevertheless, consideration of these implications is relevant for both pediatric research and pediatric medicine.

TAILORING PEDIATRIC RESEARCH TO DEVELOPMENTAL VARIABILITY

Paraphrasing a common theme in pediatrics, children are not just small research participants. At different ages from birth through adolescence, children who participate in research differ from adult research participants—and from each other.

An understanding of developmental pharmacology and the appropriate conduct of pharmacokinetic and pharmacodynamic trials is an essential element for most pediatric drug research plans. Those designing, conducting, and assessing the data from pediatric drug studies must also deal with other challenges related to developmental variability. This section outlines some of these challenges and responses to them. Later chapters provide further discussion of selected issues, including ethical considerations and the use of alternative endpoints and extrapolation.

Appropriate Drug Formulations and Drug Delivery Systems

In planning clinical evaluations of the safety and efficacy of medications in children, one early question is whether the formulation of a medicine developed for adults will be suitable for children in the age groups to be studied. If not, one element of the research program will be the development of an age-appropriate formulation or formulations. A few examples illustrate the ways in which adult formulations may be unsuitable for children.

- Children may be more resistant than adults to taking unpleasant-tasting medicines.
- Younger children may be unable to swallow adult capsule or tablet forms. They may require a liquid formulation that is practical, safe, effective, stable, and also palatable. Other options include a chewable tablet, a dissolvable powder, or a product that can achieve reliable doses when sprinkled on applesauce or a similar food.
- The appropriate amount of medication in a tablet will vary for children of different ages. A tablet with a single strength may be sufficient for adults, but tablets with different strengths may be needed for children.

- Intravenous drugs may be too concentrated for small infants (i.e., the appropriate volume for these patients is too small to measure reliably).

Preservatives, binders, and other additives that are safe for adults may not be safe in all pediatric age groups, particularly neonates and infants. The past problems with benzyl alcohol cited in Chapter 1 are a case in point. Today, unresolved issues include the safety of commonly used additives such as propylene glycol and ethanol (see, e.g., Nahata, 2009).

In the absence of appropriate pediatric formulations and pediatric labeling of medications, pharmacists may create an extemporaneous formulation that differs from the formulation provided and studied by the drug makers. Such formulations present their own problems related to stability, sterility, palatability, additive safety, and limited evidence-based guidance (see, e.g., Nahata and Allen, 2008).

An example of the research use of an extemporaneous formulation is described in the clinical review for sotalol (Betapace), which was studied in response to a request under BPCA with exclusivity granted in 2000. The FDA clinical reviewer described the compounding as follows:

> Five intact Betapace tablets (120 mg = 600 mg) were added to 120 ml of commercially obtained simple syrup (contained [*sic*] 0.1% sodium benzoate) in a six ounce amber bottle. The bottle was shaken and the tablets allowed to hydrate for >2 hours (or overnight). The tablets are shaken intermittently until the tablets disintegrated. The formulating was completed when . . . the syrup contained a fine dispersion of particles. The final concentration of the formulation was 5 mg/ml. (Karkowsky, 2000, p. 6)

Because FDA did not approve this product for pediatric use, the development of a commercial formulation did not arise. Nonetheless, the current labeling includes guidance for dosing in children, and it presents instructions for compounding an extemporaneous oral formulation that are more informative than those just described (Bayer Healthcare, 2010).

In addition to developing different formulations of a drug, sponsors may need to modify products that combine a drug and a device because combination products or delivery instruments developed for adults may not be suitable for delivering medications to children. To cite one example, measuring devices such as calibrated spoons or droppers that are suitable for use with liquid formulations for adults may not provide sufficient precision for small doses. (A different concern is that some parents may not understand that household tableware is not standardized by volume and that medications must be measured with specific devices to provide an accurate dose.) Measuring devices may also be marked in ways that do not assist with accurate dosing for either adults or children. FDA issued guidance on dosage delivery devices for liquid over-the-counter mediations in 2011 (CDER, 2011b).

To cite another example of drug delivery issues, children may not be able to manipulate safely and effectively the inhalation devices used to deliver certain asthma or other respiratory tract medications to adults. For younger children who cannot reliably

match inhalations to medication release from a handheld metered dose inhaler, companies have developed spacers or chambers that can hold the released medication so that coordinated breathing is not required.

Each new drug delivery modality requires extensive documentation from clinical trials to show that the drug is delivered as anticipated or reaches effective concentrations in children. In 2011, NIH announced funding opportunities for investigators to explore new strategies for the creation and testing of drug formulations suitable for children (NIH, 2011a). It noted a number of questions specific to the task of creating palatable formulations for children, as well as questions related to advances in drug delivery alternatives (e.g., skin patches and dissolvable oral films similar to over-the-counter breath freshener strips) and different approaches to oral delivery of medications (e.g., nanotechnologies).

In developing a written request or requirement for pediatric studies under BPCA or PREA, FDA may consider the need for a new pediatric formulation. For example, the final version of the written request for a study of terbinafine hydrochloride (Lamisil) for the treatment of tinea capitis (ringworm) specified that the sponsor use an appropriate formulation (e.g., suspension or rapid-dissolution tablets). Further, it specified the following conditions:

> If the studies you conduct in response to this Written Request demonstrate this drug will benefit children, then an age-appropriate dosage form must be made available for children. This requirement can be fulfilled by developing and testing a new dosage form for which you will seek approval for commercial marketing. If you demonstrate that reasonable attempts to develop a commercially marketable formulation have failed, you must develop and test an age-appropriate formulation that can be compounded by a licensed pharmacist, in a licensed pharmacy, from commercially available ingredients. (Beitz, 2006b)

As discussed in Chapter 3, the FDA Amendments Act of 2007, which reauthorized both PREA and BPCA, explicitly provides for a waiver of required pediatric studies if the sponsor can demonstrate why a pediatric formulation is not possible; the grounds for the waiver must be made public, however. Furthermore, FDA must report annually on the number of pediatric formulations developed, the number of such formulations not developed, and the reasons for a failure to develop a formulation. As of December 31, 2011, FDA reported the development of five pediatric formulations under BPCA and PREA (most related to studies required under PREA); the agency reported no formulations that were not developed.[3] The legislation also requires FDA to publish a notice that identifies any drug formulation that was developed, tested, and found to be safe and effective for pediatric use but that was not marketed within a year following a determination about pediatric exclusivity. Since the enactment of this provision, FDA has

[3] This information is posted and updated at http://www.fda.gov/downloads/ScienceResearch/SpecialTopics/PediatricTherapeuticsResearch/UCM194987.pdf.

posted two such notices: one for a formulation of pantoprazole sodium oral suspension for delayed release and the other for valganciclovir (formulation not specified).[4]

Appropriate Research Endpoints and Procedures

Developmental differences may entail not only the creation of different formulations of medications for use with children but also the creation of developmentally appropriate research measures and procedures that differ from those used in studies with adults. As discussed further in Chapter 5, efficacy endpoints in pediatric clinical trials may differ from the endpoints in studies with adults and may also vary across pediatric age groups.

Alternative and Surrogate Endpoints

Efficacy measures used for adults or older pediatric age groups are sometimes not suitable for use with younger age groups. For example, to study medications that are intended for the relief of symptoms such as pain or nausea, symptom scales designed and validated for use with pediatric age groups may be necessary, including different scales for early verbal children, somewhat older children, and children with intellectual or developmental disabilities (Tomlinson et al., 2010). For preverbal children, symptom measures may be based on parent or investigator assessment of facial expressions and physical movements (see, e.g., Taddio et al., 2009). Both kinds of measures of symptoms are alternatives to those used for adults.

An alternative endpoint may also be a surrogate endpoint. A surrogate endpoint in a clinical trial is a laboratory measurement or a physical sign used as a substitute for an endpoint that measures directly how a patient functions, feels, or survives. For adults as well as children, surrogate endpoints may be used in a variety of clinical research situations in lieu of endpoints such as mortality or organ failure that may occur rarely or that may develop over a period of years. Examples that have been validated for some research uses include blood pressure, exercise capacity, and cholesterol levels. FDA has recognized in various contexts the value of surrogate measures in pediatric trials. For example, in 2000 draft guidance on pediatric oncology studies, the agency emphasized that approval of a drug for pediatric use could be based on a drug's effect on tumor size or other surrogate measure that was likely to predict clinical benefit (CDER/CBER, 2000).

A particular surrogate measure may not be appropriate for children of all ages. For example, forced expiratory volume in 1 second (FEV1) is an accepted surrogate measure to assess the advance of lung dysfunction in patients with diseases such as cystic fibrosis. Although widely used in older children, it requires physical maneuvers (i.e., strongly inhaling and forcefully and completely exhaling) that can be difficult for young children and impossible for infants to perform (Castile, 2004). Training and experience

[4] This information is posted and updated at http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM203653.pdf.

may make measurement of FEV1 feasible with children as young as 5 years of age, but alternative measures and techniques are usually required for use with children less than 6 years of age. To cite another example, exercise capacity is often used as a surrogate measure in children with pulmonary hypertension or congestive heart failure, but its reliable measurement in children less than 7 years of age, who are often developmentally unable to perform the test, is difficult. This difficulty is further compounded in children with developmental delay, such as those with Down syndrome, who are predisposed to pulmonary hypertension and congestive heart failure (Walker, 2010a).

As in adults, investigators may also devise composite endpoints for pediatric trials. Each single endpoint that is included in a composite endpoint should have clinical significance and interpretability in its own right. The composite endpoint then becomes a summary measure of effect from the different variables. The rationale for using a composite endpoint in a clinical trial is that it can reduce the size of the trial if the components of the composite increase the number of events. This can be a major advantage in pediatric trials. In addition, a composite endpoint can address broader aspects of a multifaceted disease and can combine components (e.g., rehospitalization) that occur more frequently than other components (e.g., mortality). In general, these components should add to the total treatment effects, move in the same direction, be of generally similar significance, and be easily ascertained.[5]

Some studies of drugs to treat HIV infection offer an example of the use of a composite endpoint that reflects developmental considerations. Because infection with HIV can negatively affect children's growth, growth has been incorporated into composite endpoint measures for some pediatric studies of antiretroviral drugs. Although changes in weight were the initial focus, studies have suggested that changes in height are more closely related to survival (Benjamin et al., 2004).

Use of Alternative Biospecimen Sampling Procedures

Alternative research procedures may also be necessary for studies that require frequent sampling and testing of blood and other biological specimens. This sampling can be stressful for adults, who typically understand the rationale and the procedure; it can be even more stressful for children, particularly young children. For these children, their small veins also complicate the drawing of blood, and they have a smaller volume of blood, which limits the amount of blood that can be safely drawn.[6] Fortunately, technological advances allow accurate assays with smaller sample sizes than in the past.

In addition to assay innovations, the greater use of population-based pharmacokinetics permits less frequent or dense individual sampling than in traditional pharmacokinetic studies (CDER/CBER, 1999a; see also Zuppa et al., 2011). This can, for

[5] In guidance on the discussion of clinical studies in a drug's labeling, FDA has advised that "[i]n general, the results for all components of a composite endpoint should be presented. Presentation of all components reveals which components are driving the result and which components may be unaffected, or even adversely affected, by treatment with the drug" (CDER/CBER, 2006, p. 5).

[6] The institutional review boards that review research proposals for compliance with standards for human research protections (see Chapter 4) may have guidelines on acceptable blood draw volumes by weight (see, e.g., http://www.ucdmc.ucdavis.edu/clinicaltrials/documents/Blood_Draws_Maximum_Allowable.doc).

example, reduce the burden of frequent blood draws on individual children. Population pharmacokinetics can be described as "the study of variability in drug concentrations between individuals . . . [including] the assessment of variability within the population and . . . [the assessment of possible sources of] variability in terms of patient characteristics such as age, renal function or disease state" (EMA, 2009a, p. 3). The approach also allows the use of data from a variety of sources not normally used in pharmacokinetic analyses, for example, data from studies assessing the relationships between dose and efficacy or safety.

Aside from these kinds of procedural or methodological innovations, investigators studying hospitalized children may be able to obtain extra serum and plasma during clinically indicated blood sampling to allow repeat validation of an analysis without additional blood draws. Such "scavenged" samples can be used to enhance pharmacokinetic studies, especially in small premature newborns (Wade et al., 2008). In addition, pharmacokinetic studies of some drugs may be amenable to the use of samples of other bodily fluids (such as tears or urine) that can be obtained noninvasively (McCracken et al., 1980).

Children's Development and Adaptations in Research Strategies

Development-related differences such as those described above may require a variety of adaptations or additions to research plans or strategies. As discussed in Chapter 4, ethical considerations may also dictate adaptations.

Studies with Juvenile Animals

Concerns about possible toxicities not seen in adults may prompt FDA to require short-term or long-term studies involving juvenile animals. Such studies generally supplement the studies with older animals that typically precede clinical trials with adults.

For example, when FDA approved abatacept (Orencia) for treatment of juvenile idiopathic arthritis in patients ages 6 to 16 years, it deferred clinical studies for the 2- to 5-year-old age group until data from three safety studies with juvenile rats had been submitted and evaluated (Rappaport, 2008). FDA's online database for tracking postmarket study requirements shows that the data from rat studies have been submitted. (It also shows—without explanation—that FDA released the sponsor from the requirement for the deferred clinical studies with children in the 2- to 5-year-old age group.)

Studies with Different Pediatric Populations

As explained above, developmental differences within the pediatric population often require that separate clinical studies be undertaken with individuals in different age groups. For a number of the products discussed in this report, FDA required studies with

neonates; infants up to 1 or 2 years of age; one or two groups of older, preadolescent children; and adolescents. Separate studies with each age group, however, may necessitate adjustments in the research plan, for example, if suitable efficacy measures are not available for the youngest age groups.

Aside from the additional complexity and cost of separate studies, one disadvantage of separate studies for different age groups is that the separate studies may fragment what is already a small population. Although such fragmentation presents problems, one alternative—inclusion of patients covering a broader age range in a single study that is not powered for subgroup analysis by age—presents the risk that the study will fail to enroll sufficient numbers of patients in relevant age groups to identify important developmental differences in a drug's safety and efficacy.

Use of Extrapolation

Chapter 5 discusses one strategy that FDA commonly allows in an effort to encourage pediatric drug studies while reducing the costs to sponsors. Instead of specifying the two adequate, well-controlled safety and efficacy trials that are often required for studies of drugs in adults, FDA may indicate in advance that it will accept the use of extrapolation of efficacy from studies with adults to children (or from one pediatric age group to another), usually with requirements for the submission of some supportive pharmacokinetic, safety, and efficacy data.

For a particular drug and indication, the appropriate use of extrapolation depends on a careful assessment of similarities and differences between adults and children in the course of the disease and the effects of the drug. FDA may thus accept extrapolation for some age groups (e.g., adolescents) but not others (e.g., neonates).

Different Approaches to Pharmacokinetic Studies

For adults, Phase I studies often start with a small number of healthy volunteers. The studies seek to investigate a drug's pharmacokinetics in individuals not affected by a disease under study; they, therefore, carry no prospect of medical benefit to these volunteers. For pediatric drug studies, either the drug or the research procedures (e.g., extensive blood draws), or both, are often deemed to involve more than minimal risk without the prospect of direct benefit to the child. Such studies are restricted under the framework of the research protections described in Chapter 4.

As a result, with FDA and institutional review board agreement, sponsors of pediatric drug studies typically develop needed pharmacokinetic evidence by using a combination of data from previous studies with adults and new data from studies involving children who have the condition being studied. For example, the clinical pharmacology review for the drug sotolol (Betapace) included a literature review of data from studies of healthy adults, ill adults, and ill children. It also evaluated the findings from two Phase I trials (Gobburu and Canal, 2000). One of these trials was a single-dose study involving 34 children (ranging from neonates to children 12 years of age) who

needed treatment for arrhythmias. The other was a study of 25 children (in the same age range) using an ascending-dose titration design with three dose levels.

A pediatric pharmacokinetic analysis is sometimes embedded in a safety and efficacy study. For example, for the investigation of zoledronic acid (Zometa) for osteogenesis imperfecta, the pharmacokinetic study was part of the clinical safety and efficacy study (as allowed by the written request) (Vaidyanathan, 2008). One ethical rationale for this approach is that the study would have the prospect of benefit.

As described earlier in this chapter, the methods of population pharmacokinetics can minimize the burden on child research participants, for example, by collecting fewer samples per participant from a larger study population (CDER/CBER, 1998a, 1999b; Howie, 2010). This approach has ethical as well as practical and economic advantages in certain situations.

As discussed in Chapter 7, the lack of pediatric pharmacokinetic studies may contribute to unsuccessful efficacy trials. For example, FDA requested safety and efficacy studies but not a pharmacokinetic study for the use of albuterol sulfate inhalation (Ventolin HFA) aerosol to treat asthma in children ages birth up to 2 years and 2 years up to 4 years. The clinical reviewer concluded that the studies did not show efficacy and that the dose chosen for the studies might not have been optimal (Wang, 2008a).

Other Modifications in Trial Design

Among other advances in strategies for designing clinical studies, adaptive trial designs are potentially helpful in pediatric drug studies. These strategies allow certain changes in trial design based on planned analyses of data collected at interim points during a trial. As described in FDA guidance, such changes may make studies "more efficient (e.g., shorter duration, fewer patients), more likely to demonstrate an effect of the drug if one exists, or more informative (e.g., by providing broader dose-response information)" (CDER/CBER, 2010a, pp. 1–2). For example, as dose-response data accumulate during the course of a trial, analyses may indicate a lack of response or unanticipated adverse reactions for a particular dose; further use of that dose can then be stopped. To cite another example, an interim analysis may suggest the need to adjust the sample size upwards or downwards, thus avoiding either an unnecessarily large sample or a statistically underpowered study that will not provide adequate evidence about a drug's efficacy. The FDA guidance stresses the importance of careful application of these techniques to avoid the introduction of bias that compromises the validity of study results.

One example of an adaptive design in pediatrics is seen with clopidogrel (Plavix), which was investigated under BPCA for treatment of neonates and infants with cyanotic congenital heart disease palliated with a systemic artery-to-pulmonary artery shunt. The event-driven trial design included three interim analyses conducted by an independent statistician associated with the data-monitoring committee for the study. The design would have allowed the early discontinuation of the trial if the interim analyses showed a definite efficacy advantage (or a safety concern) for the test drug (Chen, 2010). As it turned out, neither the interim nor the final analyses supported efficacy. FDA also cited

problems with the sponsor's approach to certain aspects of the research that might have compromised the potential of the study to demonstrate efficacy.

Attempts have been made to devise trial architecture that is more acceptable to children and their families and that will thereby encourage enrollment. As described in Chapter 1, enrolling sufficient numbers of children is a persistent challenge for research sponsors. Parents are particularly averse to enrolling their children into clinical trials in which the children may be exposed to long courses of placebo (Caldwell et al., 2003).

One example of alternative trial architecture is the randomized withdrawal design. It has been used for a number of trials of biologic therapies for juvenile arthritis (Lovell et al., 2000, 2008; Ruperto et al., 2008). In this design, all subjects are enrolled into an open-label phase in which all subjects receive study medication. Only those participants who show a response go on to further study (which makes this an example of an enrichment design). Those responding are then randomized to continue with active therapy or to be switched blindly to placebo (i.e., withdrawn from active therapy). The main study endpoint is the proportion of participants in the two arms who maintain a response (or, conversely, the proportion who have a disease flare). This study architecture is favored by some parents and investigators since the children randomized to placebo may be switched back to active therapy (in an open-label fashion) as soon as a disease flare occurs; in this way, prolonged exposure to placebo is minimized.

Other study architectures that aim to maximize enrollment and minimize exposure to placebo include randomized dose comparison designs, the randomized placebo phase design (Feldman et al., 2001; Abrahamyan, 2011), and crossover and multiple-crossover designs.

Infrastructure for Research in Pediatric Therapeutics

The kinds of challenges outlined above have prompted efforts to create and maintain research resources to support drug studies that appropriately accommodate developmental variability. These resources include

- clinical investigators knowledgeable about developmental pharmacology and other features of pediatric research;
- physical facilities that accommodate children of different ages and their parents;
- trial design and data analysis strategies tailored to pediatric trials;
- administrative structures, including systems that support the multisite networks often required for pediatric studies to enroll sufficient numbers of children; and
- child-focused research ethics programs that include individuals with extensive experience in conducting or evaluating clinical research involving children.

Although the actions are limited in scope, considering the need, NIH has taken some steps to develop a better infrastructure for pediatric clinical trials. In 1994, the National Institute of Child Health and Human Development (NICHD) established the first national network for pediatric pharmacology (NICHD, 1998). Later, it supported the creation of the Pediatric Pharmacology and Therapeutics Research Consortium. The

announcement of funding opportunities for the latter noted the need "to address knowledge gaps that may be responsible for failed [pediatric] efficacy trials" (NIH, 2008, unpaged). In 2010, NICHD announced a contract for Duke University to create the Pediatric Trials Network to develop a stronger infrastructure for clinical trials in support of the institute's BPCA program, which focuses on high-priority studies of off-patent drugs (Berezny et al., 2011). (See Chapters 3 and 6 for a description of NICHD's role in BPCA and in setting priorities for pediatric therapeutic research, including neonatal research.)

Within the Clinical and Translational Science Awards program (which aims to speed the pace at which laboratory discoveries lead to effective treatments), a working group has focused on ways to accelerate progress in pediatric research. For the 2011 meeting of the Pediatric Academic Societies, the group helped organize a session on the BPCA. The session featured presentations of strategies for developing better predictors of outcomes in pediatric drug studies (CTSA CCHOC, 2011).

Disease-focused initiatives also play a role in supporting drug studies for pediatric health conditions. For example, the Children's Oncology Group (COG), created in 2000 through the merger of four smaller groups, is an international cooperative that each year conducts dozens of clinical trials with NIH and industry funding. Because cancer care for children is more concentrated in research institutions than is adult care, approximately 90 percent of children with cancer in the United States are treated in COG institutions. The group's cooperative research strategy has achieved relatively high rates of enrollment in trials of cancer therapies (50 to 60 percent of all eligible children and 90 percent of children under age 5 years) (O'Leary et al., 2008). Even so, achieving sufficient enrollment is often a challenge. The group places a priority on the early assessment of a drug's potential and the timely ending of unpromising trials so that limited resources—including research participants—can be most effectively allocated.

The Cystic Fibrosis Therapeutic Development Network, which is affiliated with the Cystic Fibrosis Foundation (CFF), has been an innovator in advocacy group efforts to stimulate focused drug discovery, translational, and clinical research. The network is a subset of specialized research centers drawn from a larger network of clinical care centers; it has expanded from 18 to 80 centers in recent years (CFF, undated).

Although not specific to pediatric studies, FDA's initiatives to advance regulatory science have the potential to improve such studies. As defined by FDA, regulatory science is "the science of developing new tools, standards, and approaches to assess the safety, efficacy, quality, and performance of FDA-regulated products" (FDA, 2011a). As part of the initiative for developing and refining clinical trial designs, endpoints and biomarkers, and analytic tools, the agency described needs to

- continue to refine clinical trial design and statistical methods of analysis to address issues such as missing data, multiple endpoints, patient enrichment, and adaptive designs;
- identify and evaluate improved clinical endpoints and related biomarkers for trials in areas where optimal endpoints are lacking (e.g., efficacy and safety endpoints for osteoarthritis in humans and animals, for gene therapy, for ophthalmic indications, for tumor vaccines, and for stem cell-derived therapies);

- develop novel trial designs and endpoints for special needs (e.g., small trials for orphan indications, designs and endpoints for pediatric trials including neonatal trials);
- continue to refine the use of modeling and simulation in clinical trial design to enhance the effectiveness of clinical studies; [and]
- continue development and refinement of tools and approaches for assessing benefit/risk (FDA, 2011a, pp. 11–12).

In some instances, as in the third bullet above, FDA explicitly notes the relevance of initiative elements to pediatric studies. To the extent that those involved in implementing the initiative for clinical trials consider developmental issues and solicit pediatric expertise, it should in the future yield improvements in the value of pediatric studies requested under BPCA or required under PREA.

SHORT-TERM STUDIES AND LONG-TERM CONCERNS

Most studies used to support the approval of drugs by FDA are relatively short term, lasting for a few days, weeks, or months, even for drugs that are used for years in the treatment of chronic conditions such as asthma, diabetes, and autism. The scarcity of long-term studies of medication effects is a concern for both adult and pediatric populations.

For children, however, an added concern is how drugs used either acutely or chronically may affect growth and development or have late adverse effects. Even relatively short-term use may be associated with adverse effects years later. One reasonably well-understood example involves drugs that help save the lives of young children with cancer but create risks for later problems, including cognitive limitations, fertility impairment, or new cancers (NCI, 2011).

Even when FDA identifies long-term growth and development or other safety issues, it may not include long-term studies in a written request or require longer-term postmarket studies after approving use of a drug by children. For example, in requesting studies of the use of aripiprazole (Abilify) for treatment of schizophrenia in adolescents, FDA noted concerns about the effects of the drug on growth and development and encouraged but did not specify long-term studies (Behrman, 2003). Some time later, when the agency approved the drug for acute treatment of irritability associated with autism, it did require a long-term efficacy and safety study for maintenance treatment for the condition (Laughren, 2009a).

The unclear risk-benefit ratio of the long-term use of some chronic medications may raise questions about when such agents should be started, particularly when the events that they are intended to avert would not be expected to occur for many years. Thus, in an editorial discussing statins and children, Stein (2007) suggested that "given the residual uncertainty of the impact on safety, growth, and sexual development in the younger age groups and the fact that clinical events do not appear until the mid to late 20s at the earliest, it would still appear prudent to delay the start of statin and other lipid-lowering drug therapy until the age and sexual development stage outlined by the recent AHA [American Heart Association] consensus statement" (p. 595).

FDA must balance the benefits of facilitating the entry to the market of products showing short-term benefit against the risks of long-term harm. It must also consider the possibility that the incentives of BPCA may not be sufficient to attract positive responses from sponsors when a request involves a long-term study. Chapters 5 and 6 also note the need for long-term studies of drugs. Chapter 5 suggests that FDA could make greater use of its authority to require long-term safety studies when it approves a product for pediatric use.

CONCLUSIONS

This chapter has provided an overview of developmental pharmacology as a basis for designing, conducting, and evaluating pediatric drug studies. It has discussed how children's growth and development may require alterations in research strategies that are commonly used in conducting drug studies with adults.

The exclusivity incentive and other features of BPCA and PREA explicitly recognize and accommodate some distinctive features of pediatric research. Notably, with direction from Congress and on its own initiative, FDA has added to its staff individuals with expertise in pediatrics and pediatric research to support oversight of pediatric study requests or requirements, discussions with sponsors about acceptable research designs, and appropriate review of submitted pediatric data (see Chapters 3 and 4). By employing sufficient expertise in developmental pharmacology and pediatric clinical research from the early stages of pediatric plan discussion through the review of submitted studies, FDA increases the likelihood that studies will generate useful information to guide and improve clinical care for children of all ages.

The next chapter moves from developmental variability and pediatric research to public policy. It builds on the overview provided in Chapter 1 to discuss BPCA and PREA in more detail.

3
Policy Framework for BPCA and PREA

The incentives of the Best Pharmaceuticals for Children Act (BPCA) and the requirements of the Pediatric Research Equity Act (PREA) and their predecessor policies apply within a broader framework of statutes and regulations that are intended to protect public health by ensuring the safety and effectiveness of medications. The foundations of BPCA and PREA are the Federal Food, Drug, and Cosmetic Act (FDC Act), elements of which apply to biologics as well as conventional drugs, and the Public Health Service Act (PHS Act), which includes additional requirements specific to biologics. When Congress passed the Biologics Price Competition and Innovation Act (BPCIA) (as part of the Patient Protection and Affordable Care Act of 2010, PL 111-148), it extended the provisions of BPCA to cover biological drugs.

Although both BPCA and PREA refer to the pediatric population, neither statute nor the implementing regulations define the age range or subgroups to which they apply. As noted in Chapter 1, the Food and Drug Administration (FDA) has described the pediatric population as including individuals ages "birth to 16 years, including age groups often called neonates, infants, children, and adolescents" (CDER/CBER, 2005, p. 8). Elsewhere, the agency has proposed age ranges for these groups. In application, when it requests or requires pediatric studies of specific products, FDA considers what age ranges are appropriate given the medical condition to be studied, the research questions and procedures, and, possibly, the characteristics of the drug in question.

This chapter begins with a brief overview of the regulatory context for BPCA and PREA, including definitions of key terms, procedures governing the study and approval of new drugs and biologics and their labeling, and mechanisms for monitoring drug safety after products are approved for marketing. It then describes major features of BPCA and PREA The discussion of PREA includes a short comparison of differences in requirements for pediatric drug studies between the United States and Europe. The chapter concludes with some suggestions for policy makers as they consider the reauthorization of BPCA and PREA in 2012. Chapter 4 describes another part of the regulatory framework for pediatric studies—regulations concerning the protection of human participants in research. Chapter 8 provides more information about BPCIA, the implementation of which was still in its early stages at the time this report was being completed.

BASIC REGULATORY FRAMEWORK FOR DRUG DEVELOPMENT, APPROVAL, AND SURVEILLANCE

Definition of Drugs and Biologics

As defined in the FDC Act, *drugs* are

> articles recognized in the official United States Pharmacopoeia, official Homoeopathic Pharmacopoeia of the United States, or official National Formulary, or any supplement to any of them; and (B) articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals; and (C) articles (other than food) intended to affect the structure or any function of the body of man or other animals; and (D) articles intended for use as a component of any article specified in clause (A), (B), or (C).(21 USC 321(g)(1))

This definition encompasses both small-molecule chemical compounds (what are conventionally called "drugs") and biologics.[1]

For regulatory purposes under the PHS Act, as amended by BPCIA in 2010, a *biologic* is "a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, protein (except any chemically synthesized polypeptide), or analogous product, or arsphenamine or derivative of arsphenamine (or any other trivalent organic arsenic compound) applicable to the prevention, treatment, or cure of a disease or condition of human beings" (42 USC 262(i)). A few biologics have been and still are regulated under the FDC Act. These include a small group of older products such as insulin and human growth hormone that were originally derived from human or other animal sources but that may be produced today using recombinant DNA technology. Some of these products have been the subject of written requests and pediatric exclusivity under BPCA. Examples include insulin glargine (ribosomal DNA origin) (Lantus), somatropin recombinant (Omnitrope), and hyaluronidase recombinant human (Hylenex).

Investigational New Drug Application

Under the FDC Act and the PHS Act, an early regulatory step on the pathway to product approval is the filing of an Investigational New Drug (IND) application by the sponsor (in essence, the owner) of a promising drug or biologic product. The application describes the indications (clinical uses) to be investigated, the existing data on the drug or biologic (e.g., from animal studies), and the proposed strategy for clinical testing with humans.

The IND application process is an important mechanism by which sponsors and FDA may communicate about how studies should be designed and conducted to meet

[1] In 1972, the Secretary of what is now the Department of Health and Human Services gave FDA the explicit authority to apply the requirements of the FDC Act to biologics (37 FR 4004, cited in Carver et al., 2010).

agency criteria for approval of new drugs, new indications, new formulations, or use by new populations. These communications may lead to modifications of research protocols as studies are planned or initiated.

FDA may initiate discussions of pediatric studies during the IND application process if such studies are not already being conducted under the application. These discussions may, for example, make clear that PREA requirements will be waived because the condition being studied is not diagnosed in children. Alternatively, FDA may signal to sponsors that pediatric studies will be required, and it may encourage them to start planning for those studies and to be ready to begin them as early as possible taking safety into account (see discussion of the pediatric plan below).

New Drug Application or Biologics License Application

Before a product may be marketed, the sponsor typically must submit a New Drug Application (NDA) or Biologics License Application (BLA). These applications encompass volumes of documentation for FDA review and scrutiny. FDA reviews and approves a range of details related to the drug or biologic. These details cover the active and inactive ingredients of the components of the drug or biologic; packaging materials; container-closure systems; methods, facilities, and controls for product manufacturing, processing, packing, and analytical testing; proposed labeling; and reports of clinical and other investigations. These investigations are conducted to show whether the product is safe and effective under the proposed conditions of use (for products covered by NDAs) or is safe, pure, and potent under the proposed conditions of use (for products covered by BLAs). Chapter 5 discusses FDA's protocols for staff assessments of safety, efficacy, and other studies submitted by sponsors to support product approvals.

Once an original NDA or BLA has been approved, FDA may approve supplemental NDAs or BLAs. Among other changes, these applications may cover such disparate modifications as the addition of a new indication to a product's labeling; the expansion of an indication to a new population of patients; the availability of a new form of the product; a change in the dosing regimen; the addition of new safety information to labeling; and a modification involving component specifications, suppliers, or manufacturing processes.

Under the FDC Act, sponsors of original and supplemental applications must provide substantial evidence of a product's safety and effectiveness for its intended use. As described in the statute, substantial evidence

> means evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof. If the Secretary determines, based on relevant science, that data from one adequate and well-controlled clinical investigation and confirmatory evidence (obtained prior to or after

> such investigation) are sufficient to establish effectiveness, the Secretary may consider such data and evidence to constitute substantial evidence for purposes of the preceding sentence. (21 USC 355(d))

In the FDA Modernization and Accountability Act of 1997 (FDAMA; PL 105-115), Congress clarified that data from one adequate and well-controlled study, together with confirmatory evidence obtained before or after that study, can constitute "substantial evidence" of effectiveness for any new drug. FDA regulations specify that studies and study reports should

- provide a clear statement of purpose;
- permit a valid comparison of the experimental group with a control group;
- employ suitable methods to assign study and control groups and otherwise to minimize bias;
- use clear, reliable methods to define and assess responses of research participants; and
- employ appropriate methods to analyze study results (21 CFR 314.126; see also CDER/CBER, 1998).

In the case of a drug reviewed under the NDA process, FDA's approval determination is based on judgment that the submitted data and information show that (1) the product will be safe for use under the conditions described in the proposed labeling; (2) substantial evidence exists that the drug will have the effect that it purports to have under the conditions of use described in the proposed labeling; and (3) the methods, facilities, and controls used for the manufacture, processing, and packing of the drug are adequate to maintain its identity, strength, quality, and purity (21 USC 355; 21 CFR Part 314). Although similar in substantive underpinnings, FDA approval of a biological drug in the BLA process is based on the sponsor's demonstration that the product is safe, pure, and potent and that the facility in which the product is manufactured, processed, packed, or held meets standards designed to ensure that the product continues to be safe, pure, and potent (42 USC 262(a)). In addition, FDA has incorporated concepts of the FDC Act into the BLA approval process by holding that a demonstration of "potency" includes demonstration of effectiveness (see 21 CRF 600.3(s) and CDER/CBER, 1998b).

Labeling Requirements

The sponsor technically owns and holds copyright to a product's labeling information, and it normally proposes and participates in labeling changes subject to close FDA oversight. The labeling of NDA and BLA products is governed by a common set of regulations (21 CFR Part 201) that are designed to make detailed and clear information available to prescribers. This prescribing information covers these broad topics:

- Drug name, dosage forms, and strengths
- Indications and usage

- Dosage and administration
- Contraindications
- Warnings and precautions
- Adverse reactions
- Drug interactions
- Use by specific populations (including pregnant women, pediatric populations, and geriatric patients)
- Drug abuse and dependence (if a concern)
- Overdosage
- Clinical pharmacology
- Nonclinical toxicology
- Clinical studies
- Storage and handling
- Patient counseling

In 2006, FDA initiated the use of a structured format and content for drug labeling that includes, among many other required elements, a front page or leading section with Highlights of Prescribing Information that cover key information about indications, usage, dosing; safety warnings and cautions of various sorts; and use by children and other special populations (FDA, 2006b). The requirements for use of this format are being phased in through 2013. They are not fully retroactive to NDAs or BLAs approved before June 2001, so some labels may remain in the old format (established in 1979), unless sponsors voluntarily revise them. Even with the new format, information relevant to use of a product by pediatric populations may be located in several sections of the structured label (e.g., in sections on dosage, clinical pharmacology, and adverse reactions as well as in the highlights section that now appears at the start of prescription labeling). This can complicate efforts to find, assess, and summarize pediatric information in product labeling.

As discussed in Chapter 1, drug and biologic labeling historically did not include consistent, substantive information about the use of drug and biologic products in pediatric patients because that information was, for the most part, not available. Although FDA required as early as 1979 that drug labels include a pediatric subsection (as part of the section on precautions), the rules did not require the development of pediatric data for inclusion in labeling. Congress passed BPCA and PREA and their predecessor policies to respond to that information deficit.

Postmarket Studies and Surveillance

FDA's role in ensuring drug safety does not end when a product is approved for marketing. (See Chapter 5 for a discussion of recent changes to requirements for reporting of adverse events during clinical trials of a product.) To monitor and learn more about drug safety in actual use, FDA uses two general strategies.

The first strategy for postmarket safety monitoring involves the periodic reporting of new safety information to FDA. Through its MedWatch system, FDA receives spontaneous reports (i.e., reports not associated with a planned clinical study) about

adverse drug events. Sponsors of drugs and biologics have specific requirements for surveillance and reporting of adverse events associated with the use of a drug, particularly events that are unexpected (e.g., not described in the product's labeling). In addition, health professionals, patients, parents, and others may voluntarily report problems. Adverse event reports to MedWatch are compiled in a computerized database, the Adverse Event Reporting System, which FDA monitors for indications of safety problems that warrant further analysis and possible response. In addition, drug and biologic sponsors operate under obligations to report significant new information (including from the published literature) that might affect the safety, effectiveness, or labeling of an approved product. This information could be included in a sponsor's annual report to FDA or provided in an expedited report. Depending on the nature of the problem identified, the sponsor's or FDA's analysis of voluntary and mandatory safety reports and other information (e.g., literature reviews) may lead to safety advisories to clinicians and consumers, to the addition of new safety information to a product's labeling, to further studies or data analyses, or to other product changes. For example, in 2009, based on analyses of adverse event reports over a 10-year period, FDA first reported on a possible association between certain cancers in children and young adults and the use of tumor necrosis factor blockers; in 2009, following further investigation and analysis, the labeling was revised to add new safety warnings (FDA, 2009b). In rare cases, a sponsor withdraws a product from the market.

A second strategy for postmarket safety monitoring involves requirements or voluntary agreements for sponsors to undertake specified further investigations of a drug or biologic following its approval. The FDA Amendments Act of 2007 (FDAAA; PL 110-85) strengthened FDA's authority to require sponsors to conduct postmarket studies, including studies to "assess a known serious risk related to the use of the drug; assess signals of serious risk related to the use of the drug; [or] identify an unexpected serious risk when available data indicate the potential for a serious risk" (21 USC 355(o)(3)(B)). In 2009, FDA adopted internal policies and procedures for developing such postmarket study requirements (CDER/CBER, 2009), and in 2011 FDA issued guidance for industry on the topic (CDER/CBER, 2011). These safety investigations may involve pediatric studies but are separate from any requirements under PREA. For example, in 2009, when FDA approved guanfacine (Intuniv) for treatment of attention deficit-hyperactivity disorder in children ages 6 up to 17 years, it required postmarket studies of cardiac toxicity in rats and reproductive toxicity in juvenile rats (Laughren, 2009b). These requirements were separate from the requirements that the agency imposed under PREA for additional studies in the 6- to 17-year-old age group (including one for a long-term study of efficacy and safety and a second one to more fully evaluate safety and efficacy in adolescents). Both sets of studies could result in the addition of information to product labeling.

FDAMA required sponsors to report annually on their progress in meeting certain types of postmarket study requirements. It likewise directed FDA to provide annual summaries based on these reports.[2]

The importance of postmarket strategies for expanding pediatric safety information is discussed further in Chapter 5. That chapter also describes the process for

[2] An FDA website allows a status search by product and type of requirement (e.g., PREA) (http://www.accessdata.fda.gov/scripts/cder/pmc/index.cfm).

1-year safety reviews that Congress initially established in 2002 for labeling changes resulting from studies requested under BPCA and then extended in 2007 for changes resulting from studies required under PREA.

BEST PHARMACEUTICALS FOR CHILDREN ACT

History of the Exclusivity Provision

The substance of BPCA predates that statute that bears the name. Congress first established the concept and rules for what is called "pediatric exclusivity" in 1997 in FDAMA. This legislation provided incentives and FDA authority to encourage the study of drug products in pediatric patients. FDAMA included a sunset, or expiration, provision that largely limited its application to NDAs submitted on or before January 1, 2002. In 2002, Congress enacted BPCA (PL 107-109) to amend and reauthorize the pediatric exclusivity program for NDAs filed on or before October 1, 2007. BPCA was again renewed and amended in September 2007 as a component of FDAAA. The current iteration of BPCA is scheduled to expire in October 2012.

As explained earlier, in 2010, Congress extended the provisions of BPCA to cover biological drugs. This legislation is discussed further in Chapter 8.

The Incentive

BPCA establishes a voluntary incentive program through which a sponsor may gain the benefit of market protection (exclusivity) as a reward for having performed pediatric studies as specified in a written request from FDA. The core incentive is a 6-month period of pediatric exclusivity that is awarded if the Secretary of Health and Human Services (through delegation to FDA):

1. determines that information about the use of a new drug by the pediatric population may produce health benefits in that population;
2. makes a written request for pediatric studies of the drug (including a timetable for the completion of the studies); and
3. concludes that the studies submitted have been completed within the specified timetable and meet the other terms of the written request.

The law does not require that studies demonstrate that a drug is safe and effective for the specified pediatric use. Indeed, in some cases, pediatric studies have yielded important negative findings and labeling changes that warn that a drug or biologic is not safe and should not be administered in specific pediatric settings.

Pediatric exclusivity is not a freestanding protection. Instead, it attaches to one or more existing periods of patent or statutory market protections. The primary objectives of these legal protections are to encourage investment in costly and unpredictable research within a legal framework that also enables broader use of existing research findings. The latter benefit is provided for by an abbreviated approval pathway that allows sponsors of

generic and other follow-on products to rely on a demonstration of the similarity of their product to products that have already been shown to be safe and effective for specific uses. In essence, exclusivity is an incentive because it delays the time at which the sponsor of a generic or other follow-on product may secure FDA approval and begin marketing a competing product for the protected use.[3]

Table 3-1 identifies the patent and statutory market protections that can be extended by 6 months with an award of pediatric exclusivity. Only the first relates to a product's patent(s). Many drugs approved under NDAs have multiple patents that can be effectively extended by pediatric exclusivity. In contrast, as a result of more limited statutory provisions applicable to biologics approved under BLAs, pediatric exclusivity does not extend the market protective effect of patents covering such products. Independent of patents are several types of market exclusivity that may be extended for 6 months by an award of pediatric exclusivity (e.g., a 7-year orphan drug exclusivity becomes a 7.5-year exclusivity).

TABLE 3-1 Underlying Patent or Exclusivity Incentives That Can Be Extended with Pediatric Exclusivity

Underlying Incentive	Type of Innovator Applications Eligible for Underlying Incentive	Original Period of Protection Based on Underlying Incentive	Market Protection if Pediatric Exclusivity Is Earned
Patent protection (gives the sponsor the ability to exclude others from making, using, or selling a patented invention; pertinent patents may cover the drug substance, formulation, or an approved method of using the drug)	NDA[a]	Varied (patent life may be up to 20 years)	Patent life + 6 months
New chemical entity exclusivity (covers the first NDA approval for a particular active chemical moiety in the United States)	NDA	FDA may not accept or begin to review a follow-on application that relies on the innovator NDA until 5 years after the innovator's	5 years + 6 months

[3] In general, delayed approval affects a generic or other follow-on product application that expressly refers to an approved innovator product as part of the basis for the second product's approval. For example, instead of having to reassess the safety and effectiveness of a product for an established use, a competitor producing a generic product may (1) demonstrate that its product has the same active ingredient, dosage form, strength, route of administration, and labeling as the innovator product and (2) provide data to demonstrate that the product is bioequivalent (i.e., has the same rate and extent of absorption) to the innovator drug. Upon this demonstration, FDA may deem the generic product to have a safety and effectiveness profile comparable to that of the innovator product for the same labeled use. Although the BPCIA established a legal pathway for the use of abbreviated "biosimilar" biologics approvals in 2010, this pathway is at an early stage of implementation within FDA (see Chapter 8).

		approval was issued (the timeline may be 4 years if certain patent scenarios exist)	
New conditions of use exclusivity (protects an innovator's new conditions of use for a previously approved active moiety when clinical research was required to be performed to achieve the new approval, e.g., FDA approves a new indication for use, potentially including a pediatric indication, or certain other changes)	NDA	FDA may accept and review a follow-on application during the 3-year period but may not formally approve that application for the protected conditions of use until 3 years after the innovator's new conditions were approved	3 years + 6 months
Orphan drug exclusivity (covers drugs and biologics for rare diseases)	NDA, BLA	FDA may accept and review a competitor application (including that of another innovator) during the 7-year period but (with certain exceptions) may not approve another application for the same product and the orphan indication until 7 years after the innovator product's approval	7 years + 6 months
Biologic product exclusivity (covers innovator biologics; see Chapter 8 for further discussion)	BLA	FDA may accept and review a biosimilar product application during part of the 12-year period but may not approve the biosimilar product application until 12 years after the first licensure of the reference (innovator) product	12 years + 6 months
Timeline for **submission of biosimilar product application** (provides period of time during which a biosimilar product applicant may not seek FDA approval that is based on reference to an existing, licensed biologic)	BLA	An applicant for a product biosimilar to an approved biologic may not submit its application until 4 years after the date on which the reference product was first licensed	4 years + 6 months

[a] By statute, patents for BLA products cannot be extended by pediatric exclusivity.

Over time, Congress has tightened the time frame for sponsors to complete pediatric clinical studies and submit reports. Originally, a sponsor might have submitted its report at a time close to the time of expiration of the underlying patent or market exclusivity to be extended by pediatric exclusivity. That created a de facto delay of competitor approvals while FDA determined whether exclusivity had been earned. (The law authorized a 90-day period for FDA review, to be counted as part of the 6-month extension if pediatric exclusivity was ultimately awarded.) In 2007, Congress revised BPCA to require that FDA make pediatric exclusivity determinations at least 9 months prior to the expiration of the underlying patent or market exclusivity to be extended. The agency is permitted up to 180 days to make its determination whether pediatric exclusivity has been earned. As a result, sponsors now must complete and submit their reports on pediatric studies more than a year before the scheduled expiration of underlying patent and market exclusivity.

Eligible Products

Under BPCA, FDA may issue written requests for pediatric studies for already-marketed products and may grant exclusivity to sponsors who meet the terms of those requests. The statute also authorizes FDA to issue requests for products that are still under initial development (i.e., still in their first IND application period). A sponsor can conduct the requested studies and submit them either as part of an initial NDA or as part of a supplemental NDA (or, as a result of provisions in BPCIA, as part of a new or supplemental BLA).

As noted in Table 3-1, exclusivity is approved for an active moiety. The definition of active moiety focuses on chemical structures. As defined in regulations, the active moiety is "the molecule or ion, excluding those appended portions of the molecule that cause the drug to be an ester, salt . . . or other noncovalent derivative (such as a complex, chelate, or clathrate) of the molecule, responsible for the physiological or pharmacological action of the drug substance" (21 CFR 314.108(a)). Different active ingredients may thus have a common active moiety.

As an example, amlodipine maleate and amlodipine besylate are considered different active ingredients, but they have the common active moiety amlodipine. It is responsible for the physiological action of the drugs, which are used to treat hypertension. After the sponsor conducted studies requested under BPCA, FDA granted pediatric exclusivity for the moiety in 2001 and a labeling change for a product containing amlodipine besylate (Norvasc) in 2004 (Throckmorton, 2004).[4]

[4] Under limited circumstances, an active moiety that has previously been approved and has already been the subject of a pediatric exclusivity award may qualify for a second period of pediatric exclusivity. FDA must issue a second written request that differs from the first request, and the sponsor must fulfill the requirements on a timely basis. The scope of the second pediatric exclusivity reward is more limited, however, and attaches only to a period of 3-year market exclusivity that may be granted for the new conditions of use studied. A second period of pediatric exclusivity would not extend any patent or other protections (e.g., orphan drug exclusivity) that may exist.

Written Requests

FDA's written request for a pediatric study is a critical component of BPCA that determines when and how a product will become eligible for pediatric exclusivity. FDA may issue a written request at any time (i.e., it need not be linked to an NDA, BLA, or supplement). A request may specify separate and different studies for different pediatric age groups. The specified studies may cover a product's pharmacokinetics (i.e., how it is absorbed, distributed, metabolized, and eliminated from the body), pharmacodynamics (i.e., how a product affects the body), safety, or efficacy. The basic features of a written request, as currently outlined by the Center for Drug Evaluation and Research (CDER), are listed in Box 3-1.

BOX 3-1
Basic Elements of a Written Request

- Types and objectives of studies to be performed
- Indications to be studied
- Age groups and numbers of patients to be studied; ethnic/minority representation
- Study endpoints, including pharmacokinetic, pharmacodynamic, safety, and efficacy endpoints (as appropriate)
- Known drug safety concerns and monitoring
- Reporting of extraordinary (unexpected) findings
- Drug information, including dosage form, route of administration, regimen, need for development of age-appropriate formulation, and documentation requirements
- Statistical information, including the power of a study(ies) and statistical analyses to be performed
- Provisions for labeling that may result from the study(ies)
- Format of reports to be submitted
- Time frame for submitting reports
- Time table to respond to the written request
- Provisions for public information about studies

SOURCE: CDER, 2011c.

Drug sponsors may submit to FDA a Proposed Pediatric Study Request that outlines their ideas for pediatric studies. FDA may modify or reject the proposal. Approximately 80 percent of issued requests start as sponsor proposals. Alternatively, FDA may initiate a written request of its own accord. Under BPCA, FDA may request a pediatric study to evaluate the same indications intended or approved for adults, but it may also request that a sponsor conduct a pediatric study for a different indication, including one not approved for adults. The latter authority is a key feature that distinguishes BPCA from PREA. As described below, FDA may (except in rare situations) mandate pediatric assessments under PREA only when making a determination about an indication(s) that it is proposed by the sponsor in an NDA or BLA submission.

FDA may amend a written request at its own initiative or in response to problems encountered by a sponsor (e.g., problem with enrolling numbers of children sufficient to match the sample size originally expected). Many requests that were issued before the passage of FDAAA were amended to incorporate provisions of that law, for example, provisions about the addition of information to the labeling.

Scope of Exclusivity

FDA has interpreted pediatric exclusivity to attach to any patent or exclusivity protections covering any of a sponsor's products containing the active moiety that was studied in children. For example, if a liquid formulation must be developed to perform a requested pediatric clinical study, the sponsor's tablets and other dosage forms containing the same moiety, for any indication, also will be awarded pediatric exclusivity (assuming that they are subject to patents or other applicable market protections that can be extended as summarized in Table 3-1). Because exclusivity attaches to the moiety and product and not the particular indication for which studies are requested, it affects all indications for which the product is already approved. Thus, when exclusivity was granted for studies of risedronate (Actonel) for children with osteogenesis imperfecta, the additional 6 months of marketing protection restricted generic competition with the product when used for its three approved indications for different forms of osteoporosis in adults.

Policy makers believed that this broad interpretation—combined with no requirement that the studies yield positive results—was necessary for pediatric exclusivity to serve as an effective market-based incentive. Given the very recent extension of BCPA to biologics and the more complex nature of biologic product molecules, it remains to be seen how FDA will interpret the scope of pediatric exclusivity in the context of biologics.

Requests for Studies of Off-Patent Products

As mentioned in Chapter 1, BPCA created a role for the National Institutes of Health (NIH) in supporting pediatric drug studies for both on-patent and off-patent drugs.[5] For drugs that are off-patent, BPCA directed NIH to create a list of pediatric therapeutic priorities and to propose written requests for studies to FDA. (The National Institute for Child Health and Human Development [NICHD] has the lead on these activities.) If FDA then issues a written request and the sponsor declines it, the agency may refer the request to NIH for study. If NIH funds the study, the entity that conducts the study would submit the results and suggested labeling to FDA for assessment. The results of at least five NIH-funded studies have been submitted to FDA (personal communication, Anne Zajicek, Chief, Obstetric and Pediatric Pharmacology Branch,

[5] According to the Government Accountability Office, one sponsor accepted a written request for study of an off-patent drug between 2002 and the end of 2005 (GAO, 2007), and no sponsor has accepted a written request for study of an off-patent drug since BPCA was reauthorized in 2007 (GAO, 2011).

NICHD, December 1, 2011). Any labeling change resulting from a submission would have to be worked out with relevant drug manufacturers.

For drugs that remain on-patent, if the sponsor declines a written request, FDA may refer the request to the Foundation for the National Institutes of Health (FNIH) for funding. (FNIH is an independent, nonprofit, congressionally-created organization that raises private funds and works with for-profit, nonprofit, and government agencies to undertake research in support of NIH's mission.) If the Foundation does not fund the studies, BPCA directs FDA to decide whether it should require the study under PREA on the basis of criteria specified by Congress. FDA has not required any PREA studies under this provision (GAO, 2011). According to the Foundation's website, which lists BPCA activities as a "past program," the Foundation raised $4 million in 2004 to support the study of on-patent drugs, and those studies are under way (FNIH, 2011).

PEDIATRIC RESEARCH EQUITY ACT

FDA promulgated its Pediatric Rule—the predecessor of PREA—in 1998. The objective was to increase the labeling information relevant to pediatric use by requiring manufacturers to provide data and information on such use under certain circumstances. When it published the Rule, FDA noted the pediatric exclusivity provisions of FDAMA but also noted perceived limitations on their scope (63 FR 66632, 66633). Specifically, they provided no incentive for sponsors to conduct studies on certain types of products, including most antibiotics, biologics regulated under the PHS Act, and off-patent drugs. In addition, given limited resources, FDA perceived that it was likely that manufacturers would choose to undertake preferentially studies of drugs for which 6 months of exclusivity would be the most valuable. This would tend to exclude drugs with relatively small markets. Sponsors would also tend to decline requests that involved expensive studies with neonates, infants, and young children. Further, the agency noted that the statute did not ensure that results of studies would be incorporated into and improve labeling. The Pediatric Rule became effective on April 1, 1999.

As described in Chapter 1, in October 2002, the U.S. District Court for the District of Columbia determined that the Pediatric Rule exceeded FDA's authority under the FDC Act and invalidated its application. In December 2003, Congress passed PREA, which included many of the provisions of the Pediatric Rule.

The Requirement

PREA applies to marketing applications involving a new active ingredient, indication, dosage form,[6] dosing regimen, or route of administration. It requires sponsors to submit, as part of an NDA or BLA, an assessment containing data that are adequate

1. to assess the safety and effectiveness of the product for the indications claimed in all relevant pediatric subpopulations and

[6] A dosage form (e.g., tablet, capsule, solution, or topical cream) is not identical to a drug formulation (i.e., the specific ingredients and composition of an individual product).

2. to support dosing and administration of the product for each pediatric age group for which the product is safe and effective.

Studies must use an appropriate formulation for each age group for which an assessment is required. That may require the sponsor to develop and test a new formulation. Products with an orphan drug designation for a rare disease or condition are exempt from PREA requirements, whether or not the product has been approved for the designated indication. As described below, FDA may waive or defer pediatric studies.

The Pediatric Plan

PREA refers to but does not define the term *pediatric plan*. In draft guidance for industry on compliance with PREA, FDA describes a pediatric plan as

> a statement of intent submitted by the applicant outlining the pediatric studies (e.g., pharmacokinetics/pharmacodynamics, safety, efficacy) that the applicant plans to conduct. The plan should also address the development of an age-appropriate formulation. It should address whether and, if so, under what grounds, the applicant plans to request a waiver or deferral under PREA. . . . Early consultation and discussions are particularly important for products intended for life-threatening or severely debilitating illnesses. For these products, FDA encourages applicants to discuss the pediatric plan at pre-investigational new drug (pre-IND) meetings and end-of-phase 1 meetings. . . . For products that are not intended for treatment of life-threatening or severely debilitating illnesses, applicants are encouraged to submit and discuss the pediatric plan no later than the end-of-phase 2 meeting. (CDER/CBER, 2005, p. 6)

FDA recommends that drug or biologic sponsors discuss their plans for pediatric assessment, potential studies, and possible PREA waiver or deferral requests early in the drug development process. If sponsors seek a deferral or waiver of pediatric studies at the time that they submit particular NDAs or BLAs that request the approval of products for adults only, the sponsors must then (as part of the marketing application) describe planned or ongoing studies, which FDA will review.

The timing of the development and confirmation of the pediatric plan has become more of an issue since the European Medicines Agency (EMA, formerly the European Agency for the Evaluation of Medicinal Products [EMEA]) issued its policies for pediatric studies. As described below, EMA requires determination of a specific plan for pediatric studies shortly after Phase I studies with adults are completed.

Deferral of Pediatric Assessments

FDA is authorized, on its own initiative or upon request of an applicant, to defer the submission of pediatric assessments for completion at some time after the drug or biologic is approved for marketing. A deferral may be authorized when

- the drug or biologic is ready for approval for use by adults before pediatric studies are complete;
- additional safety or effectiveness data should be collected before pediatric studies are initiated; or
- another appropriate reason exists.

A sponsor requesting the deferral of a pediatric assessment must certify to FDA the grounds for deferral, describe planned or ongoing studies, provide evidence that the required studies are being conducted or will be conducted with due diligence, and submit a schedule for completing the studies. The sponsor must then report on its progress annually. If the studies have not progressed, the sponsor is required to document that the studies will be conducted in a timely and diligent way. Since the reauthorization of PREA in 2007, as an accountability measure, information from the annual update on deferred studies must be made available to the public, including through FDA's website.

FDA has limited practical options for compelling the conduct or submission of a study required under PREA. For example, although FDA may declare a product misbranded, it cannot, under PREA, withdraw marketing approval for a product. The Government Accountability Office (GAO) has recommended that FDA seek additional authority and options (e.g., monetary fines) that might "send a signal to drug applicants that there are consequences when postmarketing study commitments are not fulfilled" (OIG/DHHS, 2006, p. 21).

Waiver of Pediatric Assessment Requirements

FDA is authorized, on its own initiative or upon request of a drug or biologic sponsor, to fully or partially waive the pediatric assessment requirement for all or specific pediatric age groups. Table 3-2 cites the statutory bases for such waivers and provides recent examples. (In years past, approval letters were often not specific about the rationales for a waiver or deferral.) FDAAA specified that, if FDA grants a waiver on the basis of evidence that a drug or biologic would be ineffective or unsafe in pediatric populations, then the labeling for the product must present that information.

TABLE 3-2 Reasons for Waiver of Pediatric Assessment Requirements Authorized Under PREA with Examples from Recent NDA or BLA Approvals

Reason for Waiver	Example
Necessary studies are impossible or highly impracticable (because, for example, the number of patients overall or in a specific age group is so small or the patients are	FDA waived the pediatric study requirement for gabapentin (Gralise), which was approved for treatment of postherpetic neuralgia. It concluded that the necessary studies were

geographically dispersed).	impossible or highly impracticable because "[p]ostherpetic neuralgia is generally not a condition that occurs in pediatric patients" (Rappaport, 2011b, p. 2).
Evidence strongly suggests that a drug or biologic would be ineffective or unsafe in all or specific pediatric age groups.	FDA waived the pediatric study requirement for tesamorelin for injection (Egrifta), which was approved for the reduction of excess abdominal fat in HIV-infected patients with lipodystrophy. It concluded that using the drug in "a patient population that has not yet completed growth may result in adverse events associated with supraphysiologic levels of growth hormone, including excessive linear growth" (Rosebraugh, 2010, p. 2).
The drug or biologic does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients or specific pediatric age groups and is not likely to be used in a substantial number of pediatric patients. PREA does not define "substantial number of pediatric patients," but FDA has historically used 50,000 as a reference number (63 FR 66631 at 66636).	FDA waived pediatric study requirements for the biologic azficel-T (Laviv), a suspension of autologous cultured fibroblasts expanded from a patient's skin biopsy specimen, finding that the product "has very limited applicability to pediatric patients for the improvement of nasolabial fold wrinkles because this condition occurs only in the adult population" (Witten and Malarkey, 2011, unpaged).
The applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for a specific age group have failed.	No examples through June 2010 (GAO, 2011).

If a waiver is granted because it is not possible to develop a pediatric formulation, the waiver is limited to the pediatric age groups that require the formulation. The applicant must also document why a pediatric formulation cannot be developed and the applicant's documentation must be made public, including by posting on FDA's website. As Table 3-2 indicates, FDA has not granted any waivers on this basis.

Relationship to the Pediatric Rule

PREA established that its provisions retroactively applied to an application submitted to FDA on or after April 1, 1999 (the effective date of the Pediatric Rule). The statute gave effect to waivers and deferrals that had been issued under the Pediatric Rule, and it extended deferral periods to take into account the period between the court decision overturning the Pediatric Rule and the date of enactment of PREA. A 1-year period was established for the submission to FDA of required pediatric assessments for applications submitted between April 1, 1999, and the enactment of PREA.

The committee did not find that FDA has reported on the application of this retroactive feature. Communications by FDA with sponsors about this feature are not public.

Relationship to Pediatric Exclusivity

FDA has consistently worked to allow drug sponsors to qualify for pediatric exclusivity on the basis of the performance of clinical studies that it requires under PREA. Congress affirmed its desire for this interpretation as early as the BPCA reauthorization in 2002. BPCA expressly states that, if any pediatric study is required by law and such study meets the completeness, timeliness, and other requirements established in a written request issued under BPCA, the study will be deemed to satisfy the requirements for pediatric exclusivity (and the exclusivity incentive may be earned).

Relationship to European Requirements for Pediatric Studies

As noted in Chapter 1 and above, the laws and policies administered by FDA differ from those of the EMA as they relate to requirements for pediatric drug studies. In both jurisdictions, requirements and guidance are designed to encourage and facilitate pediatric medicinal product development. For example, EMA policies provide for a 6 months Supplementary Protection Certificate extension that is equivalent to pediatric exclusivity under BPCA. Policies differ in the timing and the scope of the required analyses. These differences have practical implications for sponsors and regulators and are the subject of ongoing communication and harmonization efforts.

Another difference between U.S. and European policies involves the timing for development and submission of a pediatric study plan. EMA policies require that a sponsors submit a pediatric investigation plan (PIP) at an early stage, that is, when Phase I studies with adults are completed. A PIP considers all age groups and conditions for which a product may have utility. It includes a structured description of studies needed, waiver or deferral issues, clinical and nonclinical requirements, and formulation issues. Without a PIP, a sponsor's marketing authorization application (similar to an NDA or BLA in the United States) will not be accepted for filing.

As described earlier, FDA encourages discussions of plans for pediatric studies relevant to PREA requirements by the end of Phase II of clinical development. Under current policy, however, the formal assessment of the pediatric study plan and any request for waivers or deferrals occurs at the time that a marketing application is filed. Approval of the plan and any waivers or deferrals occurs when FDA approves an NDA or BLA.

The committee heard that the mismatch in timing of submission requirements in the United States and Europe was a problem for sponsors and a concern of FDA (BIO 2011; Dunne and Murphy, 2011; Frattarelli, 2011; PhRMA, 2011b).[7] EMA regulations

[7] In its statement to the IOM committee, BIO presented results of a survey of its members (BIO, 2011). Approximately 60 percent of respondents reported that they prepared the relevant pediatric documents at

may drive planning decisions too early (before sufficient safety information from studies with adults is available). U.S. regulations—despite FDA encouragement of earlier discussions—may allow sponsors to delay the focused consideration of the pediatric study plan and the initiation and completion of studies that would provide important information to clinicians who treat children. Moreover, sponsors attentive to EMA requirements may devise that plans that have to be revised as information from Phase II trials in adults is evaluated.

Beyond the differences in timing of the pediatric plan, the U.S. and European systems differ in other ways. For example, EMA provides a clearer description of what is expected in a pediatric plan than is provided by U.S. statutes or regulations. Further, the U.S. feasibility criterion does not exist in legislation from the European Union (EU). As a result, a study may be required in the EU but waived in the United States under PREA. Drugs with orphan designations, which are exempt from mandatory assessment requirements under PREA in the United States, are covered by European requirements. (Orphan drugs may be the subject of voluntary, written requests from FDA under BPCA.)

The European Union's Pediatric Committee (PDCO) is the counterpart to FDA's Pediatric Review Committee (see below). The PDCO exercises decision-making authority under requirements for PIPs. Unlike the FDA committee, however, the PDCO makes binding determinations in the regulatory process.

FDA and EMA have developed a framework to encourage the regular exchange of information and perspectives on scientific, policy, ethical, and other issues related to pediatric drug development in the United States and Europe. One objective is to avoid exposing children to unnecessary or premature trials; another is to harmonize global pediatric drug development plans to the extent feasible (EMA, 2009b). Individuals from FDA and EMA may attend each other's pediatric committee meetings so that they can better understand each other's policies and operations and thus communicate better. Information exchanges between PeRC and PDCO encompass

- issues specific to particular products (e.g., details of trial design, such as choice of comparator and efficacy endpoint, and plans for long-term safety monitoring);
- general issues related to pediatric drug development (e.g., early sharing of draft guidance documents); and
- safety issues (e.g., reports of adverse drug reactions and postmarket surveillance statistics and analyses).

Communication does not, however, mean that pediatric drug development programs will have identical pediatric study protocols. It also does not mean that FDA and EMA will reach the same regulatory decisions.

FDA ADMINISTRATION OF BPCA AND PREA

A variety of FDA entities are involved in the administration of BPCA and PREA. These include the review divisions within the Center for Drug Evaluation and Research

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the end of Phase I. Although respondents cited a goal of simultaneous regulatory submissions to EMA and FDA, that goal had not been achieved for various reasons, including variable responses from FDA divisions

(CDER) and the Center for Biologics Evaluation and Research (CBER). The review divisions, which are divided according to therapeutic areas, bear responsibility for the review of and decision making over whether to approve individual product applications.

Following establishment of a requirement in BPCA in 2002, FDA established and maintains the Office of Pediatric Therapeutics within the Office of the Commissioner. This office coordinates and supports all activities within FDA involving pediatric issues. Congress specified that the staff include one or more pediatric experts and also one or more experts on ethical issues in the conduct of pediatric clinical research (see Chapter 4).

In addition, two advisory committees currently participate in the analysis of pediatric drug issues. One is the internal Pediatric Review Committee (PeRC), which was mandated by FDAAA (21 USC 355d) and is led by CDER to support quality and consistency across FDA. The PeRC includes representatives of CDER, CBER, and the Office of the Commissioner. Congress specified several areas of expertise for the committee, including pediatrics, biopharmacology, statistics, chemistry, legal issues, and pediatric ethics (see Chapter 4). The PeRC consults on and reviews a wide range of pediatric issues related to BPCA and PREA. As specific examples, the PeRC

- reviews all written requests under BPCA before they are issued;
- may review the findings of studies submitted in response to such requests and make recommendations about the granting of exclusivity;
- consults with review divisions on pediatric plans and assessments under PREA and reviews requests for waivers or deferrals; and
- consults on the tracking and public availability of information about pediatric studies and labeling changes.

In 2004, as required by Congress, FDA also created a second committee, the publicly deliberating Pediatric Advisory Committee. It is one FDA's formal advisory committees and comprises external advisors. This committee makes recommendations to FDA on a number of matters, including (1) pediatric research conducted under NDAs, BLAs, and certain other provisions of law; (2) research priorities for pediatric therapeutics; (3) ethics, design, and analysis of pediatric clinical trials; (4) certain pediatric labeling changes and labeling disputes under BPCA; (5) adverse event reports for products approved under BPCA or PREA and certain other safety issues; (7) other pediatric issues or disputes involving FDA-regulated products; (8) research involving child research participants; and (9) other pediatric matters related to FDA's regulatory responsibilities.

PUBLIC ACCESS TO INFORMATION

Congress has increasingly required FDA to provide public access to information concerning the application of BPCA or PREA. Originally, documents such as written requests and, often, FDA review memoranda were not accessible to the public except through the lengthy and onerous Freedom of Information Act process. Congress and others have come to view public access to these documents to be useful to promote

consistent decision making, information sharing, and accountability of both FDA and sponsors. In addition, Congress has acted to ensure that information from pediatric studies—whether positive or negative— is, in most cases, reflected in product labeling. Moreover, as part of FDAAA, Congress required that the sponsor (or principal investigator) of FDA-regulated drugs trials (except for Phase I trials) register the trials at ClinicalTrials.gov and report the basic results of completed trials.

Table 3-3 describes the publication requirements of BPCA and PREA as they have evolved over time. Today, publication often means the posting of information online. Chapter 4 discusses public access to information as an ethical issue.

TABLE 3-3 Selected Public Information Requirements of BPCA and PREA

Statute	Publication Requirements
FDAMA (1997)	FDA is required to publish notice only when pediatric exclusivity has been awarded. It is not required to publish a written request, the fact that a request has been made, or the fact that a report on requested studies has been submitted.
BPCA (2002)	FDA must make available to the public a summary of the medical and clinical pharmacology reviews of pediatric studies conducted for an NDA supplement.
PREA (2003)	If FDA grants a full or partial waiver because of evidence that a drug or biologic would be ineffective or unsafe in pediatric populations, the information must be included in the labeling for the drug or biologic product. No requirement to publish summaries of PREA reviews exists.
BPCA (2007)	FDA must publish notice that pediatric exclusivity has been awarded no later than 30 days after the determination is made. It must also make public a copy of the written request. FDA must publish a notice identifying any drug for which a pediatric formulation was developed, studied, and found to be safe and effective in the pediatric population (or specified subpopulation) if the pediatric formulation of the drug is not introduced on the market within 1 year after exclusivity has been awarded and notice of exclusivity has been published. FDA may order certain product labeling to include information about the results of a study. FDA must track and make available to the public, in an easily accessible manner (including posting on the FDA website), information, including statistical information, concerning ▪ Pediatric studies conducted; ▪ Specific drugs and uses, including on-label and off-label indications, studied under BPCA or PREA; ▪ Types of studies conducted under such sections (including trial design, number of pediatric patients studied, and number of centers and countries involved); ▪ Number of pediatric formulations developed, number of pediatric formulations not developed, and the reasons that formulations were not developed;

- Labeling changes made as a result of studies conducted under such sections; and
- Reports submitted on or after the date of enactment of the BPCA of 2007.

Not later than 210 days after the date of submission of a report, FDA must make available to the public the medical, statistical, and clinical pharmacology reviews of pediatric studies conducted.

PREA (2007)

Annually, following the approval of a PREA deferral, the drug or biologic sponsor must submit status or progress information on the pediatric assessment. The information must promptly be made available to the public in an easily accessible manner, including through the FDA website.

If FDA grants a PREA waiver because a pediatric formulation cannot be developed for particular pediatric groups requiring such a formulation, the applicant's submission (detailing why a pediatric formulation cannot be developed) "shall promptly be made available" to the public in an easily accessible manner, including through the FDA website.

If the Secretary of the Department of Health and Human Services grants a full or partial waiver because of evidence that a drug or biologic product would be ineffective or unsafe if it was used by pediatric populations, the information shall be included in the labeling for the drug or biologic product.

FDA must track and make available to the public certain statistical information, including the number of times that the Pediatric Review Committee made a recommendation about priority review, the number of times that FDA followed or did not follow such a recommendation, and, if it was not followed, the reasons why the recommendation was not followed.

Not later than 210 days after the date of submission of a pediatric assessment, FDA must make available to the public in an easily accessible manner the medical, statistical, and clinical pharmacology reviews of such pediatric assessments, including through the FDA website.

CONCLUSIONS

During the past 15 years, Congress has created a flexible framework of incentives and requirements to increase the study of drugs and biologics for use by children. It has also responded to emerging concerns about aspects of the framework by adding or amending provisions, in particular, to ensure that information from pediatric studies becomes public and, except in unusual situations, is reflected in drug labeling. Changes have also incorporated more pediatric expertise into the review of requests and requirements for pediatric studies and the findings of the studies submitted in response.

As the 2012 reauthorization of BPCA and PREA is debated, one question is whether both policies should now be made permanent (i.e., not be subject to further time-limited extensions). Industry and others have criticized the requirement for reauthorization of BPCA (and PREA) after relatively short 5-year periods on the ground that it creates uncertainty for sponsors that are planning drug studies that will not be

completed or perhaps even initiated before new legislation that could significantly change the incentives or requirements is passed (see, e.g., BIO, 2011; GAO, 2011; PhRMA, 2011b). The GAO has reported that for the 50 drugs approved between September 27, 2007, and June 30, 2010, the average time from issuance of a written request to the FDA's completed review of the submitted studies was 6 years (GAO, 2011). Although Congress might grandfather studies already under way to insulate them from some features of future reauthorizations, such an approach cannot be assumed.

Another possible benefit of making this reauthorization permanent is that FDA might feel more confident about expending the considerable resources that are required to update and make final the guidance documents that it has issued for BPCA and PREA. This process of updating and otherwise reexamining old documents not only could result in better information for sponsors and other interested external parties but also could contribute to consistent interpretations of both laws across FDA divisions and centers.

A major advantage of retaining the reauthorization strategy (whether for 5-year or longer periods) is that provides a stimulus for Congress and others to consider explicitly the experience with BPCA and PREA following the previous legislative action and to evaluate the need for further adjustments in the policies and their administration. Statutory change does not depend on a reauthorization process, but that process likely facilitates serious examination of the kinds of problems and possible responses described in this report.

Congress might also evaluate the arguments for harmonizing U.S. and EMA regulations on the timing of the submission of the pediatric plan. Harmonization of the requirements would require action by both Congress and European authorities, but *Congress could act independently to require earlier submission of pediatric plans in the United States (e.g., at the end of Phase II studies with adults)*. If Congress is not prepared to create such a requirement, it could direct FDA to study and report on the consequences of the differences in plan submissions requirements. For example, do FDA's preferences for pediatric drug studies have less weight with sponsors now than they might if requirements were harmonized? Even if the U.S. requirement were changed, FDA would continue to defer many pediatric studies, as it does now, because a product is ready for approval for adult use. A requirement for earlier submission should, however, encourage the timely planning, conduct, and submission of pediatric studies.

The next chapter reviews policies for the protection of child participants in research and discusses ethical issues in pediatric studies conducted under BPCA and PREA. It concludes with further suggestions for modifications to FDA policies and procedures.

4
Ethical Issues in Pediatric Drug Studies

One broad principle for the conduct of pediatric drug studies is that children should not be subjected to research that is not necessary to advance knowledge relevant to child health. Another is that children should not participate in studies that are designed or conducted in ways that predictably undermine their potential to yield such advances. In either situation, children may be exposed to more than minimal risk in research without the expectation of an advance in generalizable knowledge. Thus, shortcomings in the design or conduct of pediatric drug studies that are described elsewhere in this report have ethical implications. Moreover, it is important that the exclusivity incentive and associated profit potential provided by the Best Pharmaceuticals for Children Act (BPCA) be accompanied by clear expectations that pediatric studies undertaken under the act are needed, soundly designed and executed, and public in their results.

One element of the task for the Institute of Medicine (IOM) was to assess ethical issues presented by studies requested under BPCA or required under the Pediatric Research Equity Act (PREA). To put this task in context, this chapter briefly reviews the federal regulatory protections provided to child participants in research and describes the resources available in the Food and Drug Administration (FDA) to provide guidance on ethical questions related to pediatric studies. It then considers several specific ethical issues, including the public availability of information from clinical trials, the enrollment of healthy children in pharmacokinetic studies, and the use of placebo controls in pediatric trials.

REGULATORY REQUIREMENTS FOR PROTECTION OF HUMAN RESEARCH PARTICIPANTS

As described in Chapter 1, deaths and other harms resulting from the use of drugs not studied in children have underscored the need for policies that encourage or require the testing of drugs for safety and efficacy with pediatric use. Such testing comes with its own risks and associated debates about what constitutes an acceptable risk. For example, following a study of chloramphenicol and two other antibiotics in the late 1950s (see discussion in Chapter 2), trial investigators were criticized for failing to stop further administration of the drug after early evidence of excess fatality rates was collected in the chloramphenicol arms of the trial. The argument at the time was that continuation of the

trial was necessary to provide convincing evidence that the drug was unsafe (Murphy, 2000). Such debates, as well as examples of ethical lapses in clinical and other research involving both adults and children, have contributed to the adoption of general protections for all participants in clinical research and to the creation of special protections for children.

General Protections

The special protections for children in research function in the context of broader protections for all human research participants. Today, all clinical research regulated by the FDA, regardless of source of funding and auspices, must meet certain ethical standards (21 CFR 50 and 56). FDA's rules are similar but not identical to the regulations of the U.S. Department of Health and Human Services (HHS) that cover research conducted or funded by the department (45 CFR 46).

FDA regulations require several determinations about possible research harms and benefits (Box 4-1). Except for the last element, the determinations apply to all human research covered by the regulations. Although sponsors, investigators, and regulators also have responsibilities for weighing and minimizing risks, institutional review boards (IRBs) are panels created under regulations for the purpose of reviewing human research conducted or funded by HHS or regulated by FDA. The primary responsibility of IRBs is to protect the rights and welfare of human research participants.

BOX 4-1
Determinations of Research Risks and Potential Benefits Required by FDA Regulations

Are risks to research participants minimized by using procedures that are consistent with sound research design and that do not unnecessarily expose participants to risk and, whenever appropriate, by using procedures already being performed for diagnostic or treatment purposes? 21 CFR 56.111(a)(1)

Are risks to participants reasonable in relation to anticipated benefits to participants and to the importance of the knowledge reasonably anticipated from the research? 21 CFR 56.5111(a)(2)

Is the selection of research participants equitable, taking into account the purposes of the research, its setting, and the special problems of research involving vulnerable populations, such as children? 21 CFR 56.111(a)(3)

Are appropriate provisions for monitoring participant safety made? 21 CFR 56.111(a)(6)

Are appropriate provisions for protecting participant privacy and confidentiality made? 21 CFR 56.111(a)(7)

Does the research meet the regulatory criteria for studies involving children, including those requiring parental permission and, as appropriate, child assent? 21 CFR 50.51-54

SOURCE: Adapted from IOM (2004).

The responsibilities of sponsors under FDA regulations include selecting qualified investigators and monitoring research conduct, for example, to confirm that investigators have secured approval of trials from the appropriate IRBs. As described in Chapter 3, sponsors must submit an Investigational New Drug (IND) application before they can ship investigational drugs or biologics across state lines and begin human research. The IND process requires conformance with FDA regulations, and applications include a signed statement (Form 1572) from investigators confirming that they will comply with these regulations (FDA, 2010b).

In addition to the rules for the protection of research participants, FDA is concerned about the scientific and ethical integrity of data from clinical trials. For example, as described later in this chapter, the agency conducts routine audits of data integrity in clinical trials.

FDA also has conflict-of-interest policies that are intended to protect the integrity of research from bias arising from the financial relationships of investigators. The policies require sponsors either to certify that investigators for studies submitted in support of FDA approval had no financial interest in the studied product or the sponsor (e.g., by holding company stock) or to report the financial interests disclosed by the investigators. FDA then reviews disclosures to assess whether the interests had the potential to bias the findings of the research. A thorough discussion of conflict of interest in pediatric drug studies is beyond the scope of this report, but the financial significance of such studies not only to sponsors but also to many academic programs and investigators and to some community-based physicians does raise concerns about the potential for bias in the design, evaluation, and reporting of research.

Studies Conducted Outside the United States

The IND application process is mandatory for studies conducted within the United States. For studies conducted outside the United States, sponsors may chose to conduct the study under an IND application.

Alternatively, under regulations issued in 2008 (73 FR 22800), FDA may accept results from foreign studies not conducted under an IND application if the studies conform to the terms of good clinical practice specified by the International Committee on Harmonization (ICH, 1996). The regulations define good clinical practice as "a standard for the design, conduct, performance, monitoring, auditing, recording, analysis, and reporting of clinical trials in a way that provides assurance that the data and reported results are credible and accurate and that the rights, safety, and well-being of trial subjects are protected, including review and approval by an independent ethics committee (IEC), and provided that FDA is able to validate the study data through an onsite inspection, if necessary" (21 CFR 312.120(a)(i)). The 2008 regulations replace earlier rules that specified that international trials conform to the standards of the Declaration of Helsinki.

The amount of clinical research conducted outside the United States has grown substantially in the past several decades. An analysis of trials registered at ClinicalTrials.gov (a clinical trials registration database that is described further in

Chapter 8) found that as of November 2007, one-third of Phase III trials sponsored by the 20 largest U.S. pharmaceutical companies were conducted entirely at foreign sites and the majority of actual study sites were outside the United States (Glickman et al., 2009). An analysis of published reports of studies conducted for pediatric exclusivity from 1998 to 2007 found that 65 percent of the studies that reported study locations had at least one site outside the United States, 38 percent had at least one site in a developing/transition country, and 11 percent had no U.S. sites (Pasquali et al., 2010; see also Dunne et al., 2011a, and Maldonado et al., 2011).

The globalization of research has raised questions about the adequacy of FDA and sponsor oversight of foreign studies and the adequacy of protections for research participants in certain countries (see, e.g., NBAC, 2001, and OIG/HHS, 2001).[1] These questions involve, among other issues, possible inadequate review for conflicts of interest and possible inappropriate inducements for parents to permit their children's participation in research. Another concern involves the ability of sponsors and lead investigators to monitor studies that involve very large numbers of widely dispersed trial sites.

Drug studies conducted in other countries may also raise questions of fairness or justice. This may happen when research in developing countries exposes the research participants to risk but the primary future benefits of the knowledge gained will accrue to patients in wealthier countries because the new drugs will not be affordable in the countries where they were studied (NBAC, 2001; Glickman et al., 2009). Moreover, pharmaceutical research taken as a whole may neglect diseases that are common in poor countries and rare in wealthier countries, a reality that has prompted a variety of international initiatives to increase research on specific neglected diseases, such as malaria, leishmaniasis, and schistosomiasis (see, e.g., Hotez et al., 2007; USAID, 2009; and WHO, 2011b).

In the studies assessed by the IOM committee, one specific ethical issue in a pediatric trial appeared to be related to shortcomings in the conduct of a trial at an international site. In that case, the clinical reviewer stated that efficacy data on the prevention of maternal transmission of HIV infection were not evaluated, in part because the trial protocol did not incorporate the accepted standard of care for these study participants (Ayalew, 2002). FDA did, however, approve the addition of pharmacokinetic and safety information to the labeling of the products generated by the trial component that investigated treatment of HIV-exposed or infected neonates. This component had been the subject of a written request from FDA (Kweder, 1999).

Equity in international research is an important and complicated ethical issue that could not be effectively considered in the context of this study or on the basis of the documents that the committee reviewed. Because children are a vulnerable population, particular vigilance is important to ensure the ethical conduct of international pediatric research.

[1] In one clinical review for the drug lamotrigen (Lamictal), the reviewer noted that many studies were in countries in which the FDA had little experience (Katz, 2009; http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM187171.pdf). Concerns about data integrity led to extensive discussions with the sponsor about its site inspections and to requests that the sponsor conduct further data analyses, which FDA staff reviewed before concluding that reasonable explanations for discrepancies in data among sites existed.

Special Protections for Children in Research

Beyond the general protections described above, both HHS and FDA regulations establish special protections for child research participants that extend beyond those applicable to adults. (For HHS, the regulations are found at Subpart D of 45 CFR 46; for FDA, they are found at 21 CFR 50.1–50.4.) Although HHS first issued its regulations in 1983, FDA did not explicitly adopt the special protections until April 2001, as required by the Children's Health Act of 2000 (PL 106-310). As summarized in Box 4-2, the FDA (and HHS) regulations define four categories of research involving children that IRBs can approve. As an example of how the regulations may limit studies that are permitted for adults, these definitions would probably preclude the participation of healthy children in pharmacokinetic studies that involve more than minimal risk.

BOX 4-2
Categories of Clinical Research Involving Children That Are Approvable Under 21 CFR 50

- Clinical investigations that involve not greater than minimal risk (50.51)

- Clinical investigations that involve greater than minimal risk but present the prospect of direct benefit to individual subjects such that (a) the risk is justified by the anticipated benefit to the subjects and (b) the relation of the anticipated benefit to the risk is at least as favorable to the subjects as that presented by available alternative approaches (50.52)

- Clinical investigations involving greater than minimal risk and no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subjects' disorder or condition and (a) the risk represents a minor increase over minimal risk; (b) the intervention or procedure presents experiences to subjects that are reasonably commensurate with those inherent in their actual or expected medical, dental, psychological, social, or educational situations; and (c) the generalizable knowledge is of vital importance for the understanding or amelioration of the subjects' disorder or condition (50.53)

- Clinical investigations not otherwise approvable that present an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children as agreed to by the Institutional Review Board and the Commissioner of the FDA after consultation with a panel of experts (50.54)

SOURCE: IOM (2004).

Approvals of research involving children are also contingent on adequate provisions for parental permission for a child's participation in research and, when appropriate, the assent of that child to such participation. Under the regulations, "children" are individuals who are not of legal age to consent to research as defined in the laws of the jurisdiction in which the research is to be conducted. Despite some uncertainty and disagreement about the concept of assent and its meaningfulness in actual research settings when a child's parents favor participation, a 2004 IOM report argued

that it is desirable to involve children in research discussions and decisions—consistent with their maturity and psychological state. Doing so "respects their emerging maturity, helps them prepare for participation in research, gives them an opportunity to express their concerns and objections, and, possibly, allows them to influence what happens to them" (IOM, 2004, p. 7). Research is limited but suggests that practices concerning assent vary in actual pediatric trials (see, e.g., Olechnowicz et al., 2002, and Ungar et al., 2006).

Making decisions about the four categories of approvable pediatric research defined in the HHS and FDA regulations necessarily involves subjective judgments about the risks and potential benefits to children of clinical studies. What is minimal risk? What is a minor increase over minimal risk? Can data help inform judgments about risk? (See, e.g., Wendler et al., 2005; Nelson, 2010; and Roth-Cline et al., 2011.) These and other questions have been the subjects of ongoing debate both generally and with respect to specific research protocols. The 2004 IOM report cited above made several recommendations about the interpretation of key concepts in the HHS and FDA regulations. In brief, it recommended that investigators and reviewers of research protocols should

- "interpret *minimal risk* in relation to the normal experiences of average, healthy, normal children" and "focus on the equivalence of potential harms or discomfort anticipated in research with the harms or discomfort that average, healthy, normal children may encounter in their daily lives *or* experience in routine physical or psychological examinations or tests;
- "interpret *minor increase over minimal risk* to mean a slight increase in the potential for harms or discomfort beyond minimal risk" and "assess whether the research procedures or interventions present experiences that are commensurate with, that is, reasonably comparable to, experiences already familiar to the children being studied";
- "consider the risk of harms or discomfort in relation to the ages of the children to be studied and assess the duration as well as the probability and magnitude of potential harms or discomfort in determining the level of risk"; and
- interpret *condition* to mean "a specific (or a set of specific) physical, psychological, neurodevelopmental, or social characteristic(s) that an established body of scientific evidence or clinical knowledge has shown to negatively affect children's health and well-being or to increase their risk of developing a health problem in the future." (IOM, 2004, p. 17)

In addition, in evaluating whether to approve research that involves a minor increase over minimal risk and no direct benefit to a child with a condition or disorder, IRBs should find that "the research is likely to generate vital knowledge about the children's disorder or condition" (IOM, 2004, p. 18). The research should not "unjustly single out or burden any group of children for increased exposure to research risk on the basis of their social circumstances" (p. 17). In situations in which some research procedures have the prospect of direct benefit and others do not, then "the potential

benefits from one component of the research should not be held to offset or justify the risks presented by another" (p. 17).

The issue of excessive risk has arisen in the context of the one written request for the pediatric study of an off-patent drug that was accepted by the sponsor (NICHD, 2008). Although the drug, lindane, was also on the BPCA priority list for the National Institutes of Health (NIH) (see Chapter 3), an NIH advisory group described it to be too toxic—on the basis of existing evidence—to be ethically studied in children (NICHD, 2003). The rationale for the request was that despite label warnings about its toxicity, the drug did have considerable pediatric use for scabies; thus, dosing and safety studies might yield information to guide this use. As far as the committee is aware, the requested studies have not been undertaken. (One study registered at ClinicalTrials.gov describes a completed study of an alternative product that also included an assessment of the incidence of use of lindane [ClinicalTrials.gov identifier: NCT00604084].)

FDA ORGANIZATIONAL RESOURCES TO SUPPORT ETHICAL STANDARDS IN PEDIATRIC RESEARCH

FDA has developed generally available resources to promote ethical standards for studies undertaken to support approvals of medical products. It has also created resources specific to pediatric studies. The discussion in this section starts with the latter.

Expertise in Pediatrics, Pediatric Research, and Research Ethics

In 1999, FDA created a pediatric advisory subcommittee to its Anti-Infectives Advisory Committee. Among other issues, the subcommittee advised on ethical questions in pediatric studies. In 2004, as provided for by BPCA of 2002 and PREA of 2004, FDA created the publicly deliberating Pediatric Advisory Committee (69 FR 46098). This committee, in turn, created a subcommittee on ethics that continues. Among other issues, the Pediatric Advisory Committee and its subcommittee may be asked to consider whether studies not otherwise approvable under 21 CFR 50 should be recommended for approval by the FDA Commissioner under Section 50.54 (FDA, 2006c).[2] In addition to specific study proposals, the ethics subcommittee has considered broader topics. One recent example is the status of clinical studies that might, in the future, involve the exploratory administration of subtherapeutic doses, or "microdoses" of investigational products to children (Nelson, 2011b).

In 2002, when Congress directed the creation of the Office of Pediatric Therapeutics at FDA, it specified that the office would have at least one person with "expertise concerning ethical issues presented by the conduct of clinical research in the pediatric population" (21 USC 393a). The Office of Pediatric Therapeutics currently includes two pediatric ethicists as well as other members with expertise in pediatrics.

[2] The process is rarely used. One example that came before the FDA Commissioner in 2004 involved a proposed study involving a single dose of dextroamphetamine for attention deficit-hyperactivity disorder. It was recommended for approval by the Pediatric Advisory Committee but was withdrawn before final action (SACHRP, 2005).

These resources are available to staff of the Center for Drug Evaluation and Research (CDER) and the Center for Biologics and Research (CBER) as well as staff of the Center for Devices and Radiological Health (CDRH).

In addition, the Pediatric and Maternal Health Staff within the Office of New Drugs at CDER provides pediatric expertise to assist that center's review divisions. At both CBER and CDER, approximately 15 to 20 percent of medical officers are pediatricians (personal communication, Catherine Lee, Office of Pediatric Therapeutics, FDA, November 21, 2011). Such expertise is relevant not only to the valid and reliable assessment of scientific questions but also to the assessment of age- and condition-specific risks required by the special protections for child research participants.

As described in Chapter 3, in 2007 Congress provided for an internal FDA committee to review written requests and pediatric studies conducted under BPCA and to review pediatric plans, assessments, deferrals, and waivers under PREA (21 USC 355d). This review committee was to include expertise in pediatric ethics specifically as well as expertise in pediatrics, biopharmacology, statistics, chemistry, and legal issues. FDA created the Pediatric Review Committee (PeRC) to undertake the required reviews, which cover both scientific and ethical issues. These reviews frequently result in recommendations for significant changes in study plans, including recommendations for changes in inclusion criteria, additional adult or animal studies, or modifications in trial design to achieve an acceptable balance of risk and potential benefit (personal communication, Robert Nelson, Office of Pediatric Therapeutics, FDA, August 10, 2011). The agency can impose a clinical hold that delays or suspends work on studies that violate the regulations governing the protection of children in research.

In addition to topics considered during committee or subcommittee meetings, issues may be brought to the FDA pediatric ethics staff for consultation. Such consultations have covered the ethical implications of many elements of pediatric drug studies, including the definition of the pediatric population to be studied, the choice of control group, the use of invasive placebos, the requirements for parental permission and child assent, the assessment of risk and benefit, the appropriate standard of care in international studies, and the planning of first-in-children studies (i.e., when a drug or an indication has not been previously studied in adults) (personal communication, Robert Nelson, Office of Pediatric Therapeutics, FDA, August 10, 2011). The consultations have involved a wide array of specific product classes and clinical conditions, for example, long-acting beta-agonists; proton pump inhibitors in infants; antiretroviral products; growth hormones; monoclonal antibodies for respiratory syncytial virus and asthma; psychotropic medications; cognitive enhancers in Down syndrome; and stem cell therapies for diabetes mellitus, cancer, autism, cerebral palsy, and spinal muscular atrophy.

Some of the IOM committee's assessments covered studies that were requested, required, and undertaken before the resources just described were in place. Although the committee could not reasonably assess the sufficiency of past or current pediatric expertise across CDER and CBER review divisions and in the Office of the Director, this report emphasizes that such expertise is critical to the design, conduct, and evaluation of scientifically and ethically sound pediatric drug studies.

Other Resources Relevant to Research Integrity

Among other resources, FDA has developed a number of guidance or draft guidance documents on ethics and integrity in FDA-regulated trials, including guidance for IRBs and investigators about FDA policies and expectations (FDA, 2010b). The infrastructure to support the ethical conduct of research also includes the Office of Good Clinical Practices in the Office of the FDA Commissioner. This unit, among other responsibilities, administers FDA's Human Subject Protection/Bioresearch Monitoring Council.

Within CDER, the Division of Scientific Investigations (DSI) is responsible for verifying the "integrity of efficacy and safety data submitted to the FDA in support of new drug applications [NDAs] and to assure that the rights and welfare of human research subjects are protected" (*FDA Regulatory Procedure Manual* at 1-4-5; see also FDA, 2009a). (For CBER, the equivalent office is the Division of Inspections and Surveillance.) The division engages both in routine audits of data integrity in clinical trials as part of the review of NDAs and in investigations of specific complaints about the conduct of trials, including complaints about the protection of research participants. Among other tasks, a routine inspection might verify that investigators secured IRB approval(s) and parental permission. It might compare sites at which investigators have financial interests in the outcome of the trial (e.g., because they hold stock in the sponsor company) with other sites for indications that financial interests have influenced reported results. When an audit cites violations of protocols or good clinical practice, an FDA reviewer may assess these violations to determine whether they could affect study findings. The reviewer may then disallow acceptance of certain data in support of applications.

If a DSI or other investigation casts doubt on the efficacy or safety findings of a sponsor's trial of a product with adults, then the use of data from that trial as a basis for starting pediatric trials may also be cast into doubt. An example involves the drug telithromycin (Ketek), which was approved in 2004 for treatment of certain forms of acute bacterial exacerbations of chronic bronchitis, acute bacterial sinusitis, and community-acquired pneumonia; the approval specified required pediatric studies of the last two indications (Goldberger, 2004). After public disclosure of significant irregularities in a key clinical trial and questions about FDA management procedures, FDA withdrew approval for the first two indications in 2007 (Ball, 2007; Ross, 2007; see also Soreth et al., 2007). Subsequently, after public questions about the safety of pediatric studies involving the drug but also after several studies were completed, the company halted pediatric studies (Ault, 2006; Harris, 2006).

ETHICAL ISSUES IN STUDIES CONDUCTED UNDER BPCA AND PREA

An overarching ethical question for pediatric studies is whether the expected benefit of the knowledge to be gained from the research is reasonable in relation to the potential risk to child participants. This can sometimes be difficult to assess, particularly many years after the studies were conducted when the uncertainties of an earlier time may have diminished as knowledge about benefits and harms has accumulated from different sources.

During its assessments of ethical issues in studies requested and required under BPCA and PREA, the committee primarily relied on the information in clinical, clinical pharmacology, and statistical reviews prepared by FDA staff. Staff reviewers have access to the voluminous submissions of sponsor data, the record of communications between sponsors and FDA about the design and conduct of the pediatric studies, and the reports from DSI.

Except for egregious problems, the reviews and the information on which they are based are unlikely to allow assessments of certain aspects of the ethical conduct of research. These aspects include the soundness of processes for obtaining parental permission and child assent to research participation, the nature and risks of incentives offered for clinician participation (e.g., payments per child enrollee in office-based studies), and the extent and appropriateness of incentives offered to parents and children (e.g., payments for time and inconvenience and provision of gifts). The IOM committee did not search the literature to determine whether others had raised questions about the ethical status of particular studies requested under BPCA or required under PREA, although committee members were sometimes aware of such questions. In addition to examples drawn from the committee's assessments, this discussion also cites other cases that illustrate ethical questions or concerns with studies conducted under BPCA and PREA.

The first issue that the committee identified involves transparency in the form of public access to information from requested or required pediatric studies. The following discussion also describes issues of integrity or ethics that clinical reviewers have identified and notes concerns about the participation of healthy children in pharmacokinetic studies and the use of placebo-controlled trials.

Transparency, Labeling, and Dissemination

Transparency in the form of public access to information generated by studies requested under BPCA or required under PREA has ethical as well as scientific implications. It recognizes and respects the contributions that children (and parents) make by participating in research, acknowledges these research results as a public benefit, and supports the accountability of sponsors and FDA for their actions and decisions.

As described in Chapter 3, in the reauthorization of BPCA and PREA in 2007, Congress required that the results of studies requested under BPCA or required under PREA be reflected in labeling changes in most cases. It also required FDA to make public the staff clinical, clinical pharmacology, and statistical reviews associated with these changes and to make written requests public following exclusivity determinations.

Before these changes, BPCA of 2002 required posting of brief summaries of product reviews for studies requested under BPCA, but the requirement did not apply to studies required under PREA. FDA does make available some information about adult studies through Drugs@FDA. Such information, especially for studies submitted in supplemental NDAs or Biologics License Applications (BLAs) following a drug's initial approval, is not as extensive as that required for pediatric studies, and it can be more difficult to find (O'Connor, 2009).

The public information requirements of the 2007 legislation did not apply retroactively. Thus, information about studies requested under BPCA and, even more so, studies required under PREA is still restricted for products with approvals or exclusivity determinations made before the 2007 reauthorizations. Information can be requested under the Freedom of Information Act (FOIA), but that process is typically time-consuming and burdensome. Whether they are related to FOIA requests or not, many of the FDA documents consulted during the preparation of this report had significant redactions in ethically sensitive sections of clinical reviews, including overall risk-benefit assessments (see discussion in Chapter 5).

Although FDA agreed to provide the committee with redacted requests and reviews for up to 50 products, the release of such documents for some products with exclusivity but no labeling changes could occur only with the permission of the sponsor. As discussed in Chapter 6, both of the sponsors of neonatal studies of bacterial conjunctivitis for which no information was added to the label but for which exclusivity was granted in 2003 refused to provide permission. Substantial numbers of babies were studied in these trials, but that exposure has contributed only brief FDA summaries of study results to the public record at FDA.

In addition, FDA is still limited in what it can disclose about studies that have not had results submitted in connection with a labeling change application, for example, when sponsors have abandoned clinical development of a drug. One serious documented instance of this involves the drug cisapride (Propulsid), which was withdrawn from the market in 2000 (Willman, 2000; Harris and Koli, 2005). This withdrawal came some years after FDA first became concerned about the drug's risks, including its risks to children. It likewise came some years after the agency knew of sponsor trials (which had not been submitted) that showed a lack of efficacy in children. At the time that the drug was withdrawn, a spokesman for a children's hospital at which a child had died during a clinical trial of the drug said the drug "has been widely prescribed by pediatricians and pediatric specialists for the treatment of gastroesophageal reflux in children and infants due to its efficacy and presumed safety based on the adult data" (Neergaard, 2000). Citing ethical obligations, some have called for the creation of a publicly accessible database of results of abandoned trials (Rogawski and Federoff, 2011).

In addition to these issues of transparency, another concern involves the appearance in the published literature of information that appears to be inconsistent with the assessments of FDA reviewers and information in a product's label. A study by Benjamin and colleagues reported an analysis of 129 of 137 BPCA-related labeling changes that occurred by September 2007 (Benjamin et al., 2009). As summarized by the authors,

> Thirty-three products (26%) had pediatric safety information added to the labeling. Of these, 12 products had neuropsychiatric safety findings, and 21 had other important safety findings. Only 16/33 (48%) of these trials were reported in the peer reviewed literature; however, 7/16 of these publications focused on findings substantively different from those highlighted in the FDA reviews and labeling changes. (p. 180)

For studies leading to pediatric exclusivity, the authors suggest the need for a mechanism to increase the dissemination of unbiased information based on these studies (see also Benjamin et al., 2006). Given concerns that physicians do not generally read the study details or other information in drug labels and more general concerns about selective publication by sponsors, such unbiased dissemination could increase clinician awareness of important safety and efficacy findings (see Appendix B).

In this context, it should be noted that FDA reviews of pediatric and adult studies—even those that are public—are not integrated into resources such as PubMed and ClinicalTrials.gov. Thus, these evaluations may not be identified and incorporated into evidence-based reviews of clinical therapeutics.

FDA Reviewer Comments on Study Integrity and Ethics

Particularly in recent years, FDA clinical reviews of sponsor applications have included sections that variously comment on study integrity, ethics and good clinical practices, and financial disclosures or conflicts of interest. In these sections, reviewers may discuss protocol violations, sponsor affirmations about compliance with ethical principles or good clinical practices (which should subsume compliance with regulatory protections for children), and sponsor certifications about investigator financial relationships or conflicts of interest.

In general, in the clinical reviews that included sections on data integrity, financial disclosures, or ethics (with minimal redactions), the committee identified no major ethical issues based on the reviewers' assessments. Particularly for more recent reviews, these sections of the reviews did document FDA attention to the issues, which potentially reinforces adherence to standards for scientifically and ethically sound investigations. Early reviews examined by the committee omitted mention of these issues more often than recent reviews. In some cases, the committee found that review sections related to issues of study integrity had been redacted (see, e.g., Bastings, 2002). In addition, most specific information about investigator financial relationships or conflicts of interest was redacted.

A clinical review may make clear that the reviewer was relying primarily on the statements and certifications of the sponsor. For example, "[t]he applicant states that the quality of study data was assured through monitoring of investigational sites, appropriate training of study personnel, independent audits, investigational site visits, and periodic data source verification" (Roman, 2007, p. 14). Similarly, "the [sponsor's] clinical overview states that the studies were conducted in compliance with ethical principles that have their origin in the Declarations of Helsinki and in accordance with the International

Conference on Harmonization (ICH) E6 Guideline for Good Clinical Practice (GCP)" (Xiao, 2009, p. 14).

If sponsor disclosures or on-site audits identify issues, reviews may assess whether the situation (e.g., a protocol violation or a financial relationship with the sponsor) could be expected to influence study findings. For example, in connection with an application submitting requested studies of valganciclovir hydrochloride (Valcyte), DSI's routine, on-site investigations found a number of protocol violations. In the clinical pharmacology review, the reviewers discussed each type of violation and determined that some information submitted by the sponsor could not be accepted but that other protocol violations would not be expected to affect conclusions (Krudys and Arya, 2008). After additional information was submitted, FDA approved the drug for prevention of cytomegalovirus (CMV) disease in children aged 4 months or over who received kidney or heart transplants and were at high risk for developing the disease.[3]

Pharmacokinetic Studies with Healthy Children

As described in Chapter 2, pharmacokinetic studies undertaken with children typically differ from those undertaken with adults. For adults, Phase I studies often start with a small number of healthy volunteers. The studies seek to investigate a drug's pharmacokinetics in individuals not affected by a disease under study; therefore, they offer no prospect of medical benefit to these volunteers. For children, if either the drug or the research procedures (e.g., extensive blood draws), or both, are deemed to involve more than minimal risk without the prospect of direct benefit to the child, then healthy children should not be enrolled in such studies. Such studies are restricted under the regulatory framework described earlier, thus necessitating the use of alternative types of analyses, such as pharmacokinetic studies involving children with the condition under investigation or studies undertaken as part of an efficacy and safety trial.

Although most pediatric pharmacokinetic studies do not include healthy children, exceptions exist. For example, for a pharmacokinetic study of almotriptan (Axert), investigators recruited what were described to be healthy adolescent and adult subjects, with or without a history of migraine; of the adolescents recruited, only 2 of the 18 had a history of the condition (Harris, 2009). The original written request for a study of this drug specified a study of adolescents with a history of migraine (Behrman, 2001a); the clinical and clinical pharmacology reviews did not comment on the inclusion of adolescents without a history of migraine. The clinical review noted that the triptan drugs are generally considered to be safe but also noted concerns about cardiac and other risks. As presented for IRB review, the study protocol should have been clear that healthy children could be recruited for the pharmacokinetic study and the review should have

[3] As amended, the written request (which derived from a sponsor proposal) sought pharmacokinetic and safety studies but not efficacy studies for three categories of transplant patients and a pharmacokinetic and safety study for neonates with congenital CMV disease (Pikis, 2009). Because the latter condition does not occur in adults, the clinical review explained that efficacy could not be extrapolated and, thus, that FDA could not approve use of the drug for that indication.

considered whether such a study presented no more than minimal risk to healthy children.[4]

Use of Placebo-Controlled Pediatric Trials

The use (and nonuse) of placebo controls may present ethical questions in both pediatric and adult clinical trials, and ethicists, governments, investigators, and others have sought to provide principles to guide the use of such controls. For example, the Declaration of Helsinki, as amended, states:

> The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best current proven intervention, except in the following circumstances:
> - The use of placebo, or no treatment, is acceptable in studies where no current proven intervention exists; or
> - Where for compelling and scientifically sound methodological reasons the use of placebo is necessary to determine the efficacy or safety of an intervention and the patients who receive placebo or no treatment will not be subject to any risk of serious or irreversible harm. Extreme care must be taken to avoid abuse of this option. (WMA, 2008, p. 5)

What constitutes compelling and scientifically sound reasons for the use of placebos in adult trials is a subject of debate (see, e.g., Temple and Ellenberg, 2000; Miller and Shorr, 2002; and Temple and Meyer, 2003). FDA no longer specifies adherence to the declaration as a standard for international clinical trials (73 FR 22800). Rather, studies are to be conducted consistent with the good clinical practice standards cited earlier.

Because children are a vulnerable population and because many challenges surround parental permission and child assent for a child's participation in research, particular caution is needed when placebos are employed in pediatric trials. When the use of a placebo control in a pediatric clinical trial is proposed or contemplated, several questions warrant consideration.

- Is the condition to be studied one for which one or more therapies have been demonstrated to be safe and effective in the pediatric age group to be studied? In these

[4] Other historical examples of pharmacokinetic studies with healthy children can be cited. FDA has accepted pharmacokinetic studies of cold medicine combination products (ibuprofen and pseudoephedrine hydrochloride) that enrolled healthy children (ages 4 to 11 years in one study [Abedowale, 1999] and ages 6 to 11 years in the other [Adebowale, 2002]). One justification for such studies is that it is healthy children who get colds and whose parents may then treat them with these products. Nelson (2010) has suggested empirical criteria for identifying healthy children who are candidates for research participation on the basis of their high risk for colds (e.g., their past frequency of colds). To cite another example of healthy children in pharmacokinetic studies, at the time that it was approved in 1998, the antibiotic rifapentine (Priftin) had labeling that described the results of a pharmacokinetic study with healthy volunteers ages 12 to 15 years that yielded results similar to those found for adults (Sanofi-Aventis, 2009). See also Marshall et al., 1999 (abstract).

cases, comparative effectiveness, superiority, or inferiority trials may be more appropriate than placebo-controlled studies.

- What would be the expected harm of forgoing the use of such an existing therapy and using a placebo instead, taking into account what is known about the safety and efficacy of that therapy? Omission of a proven treatment may harm a child, so investigators and IRBs must ask whether that harm involves no more than a minor increase over minimal risk.
- Does the study design require that children who are currently receiving an effective therapy have that therapy withdrawn, or is the placebo to be used concurrently with such a therapy in one arm of the trial?

In the written requests and studies that were reviewed for this report, placebo-controlled trials of efficacy were fairly common. For example, among the sample of 45 labeling changes that the committee assessed,[5] trials with both an active comparator and a placebo control were undertaken for 3 products, at least one placebo (only)-controlled trial was performed for 22 products, and active comparators (only) were used for 7 products. For the remaining labeling changes, situations varied, involving, for example, FDA acceptance of extrapolation of efficacy from adult studies with no requirement for a controlled trial of efficacy.

The conditions investigated in active comparator-controlled trials included, in some cases, conditions that were also studied in placebo-controlled trials, for example, asthma and osteogenesis imperfecta. Other conditions studied with active comparators included certain bacterial infections and Kawasaki disease. FDA has not necessarily approved the comparator drugs for pediatric use. Examples, discussed in Chapter 6, include requested studies of bacterial conjunctivitis in neonates.

The conditions studied in placebo-controlled pediatric trials included asthma, anxiety, hypertension, schizophrenia, mania associated with bipolar disorder, migraine, osteogenesis imperfecta, attention deficit-hyperactivity disorder, and juvenile rheumatoid arthritis. At the time of some of the placebo-controlled trials, no treatments had been approved by FDA (for the pediatric age group studied) for the condition under study (e.g., irritability associated with autism). The use of placebo controls in these studies does not create the potential for harm by depriving a child of a therapy demonstrated (or widely thought) to be effective and thus does not raise ethical concerns.

In other cases, effective treatments were approved and children were taken off effective treatments. For example, effective treatments for asthma were available at the time that some of the pediatric placebo-controlled trials were undertaken.[6] A review published in 2004 examined rates of exacerbation and related participant withdrawal from trials in 45 placebo-controlled trials that did not specify the use of anti-inflammatory drugs in all those participating (Coffey et al., 2004). The review concluded that withdrawals and exacerbations were more frequent in the placebo groups. Of the 45 trials, 14 enrolled only children; the other 31 included both adults and children. The child-only trials showed the same pattern of higher numbers of withdrawals and

[5] See Appendix A for a description of how the committee selected its sample.

[6] In 1991, the National Heart, Lung, and Blood Institute issued guidelines that advised that anti-inflammatory medications be used for both children and adults who had more than mild asthma (NHLBI, 1991); updates followed in 1997 and 2004 and most recently in 2007 (NHLBI, 2007).

exacerbations in the placebo groups. Subgroup analyses were not reported for the children in trials that combined adults and children. This omission of subgroup analyses by age—and, thus, the omission of child-specific data—also raises ethical concerns. As the authors of the review observe, children in these studies were "being exposed to the risks and harms of research, but there is no advance in pediatric medicine from their participation" (Coffey et al., 2004, p. 91).

In pediatric hypertension, another condition for which effective treatments (e.g., diuretics) were also available at the time of placebo-controlled pediatric studies, investigators examined adverse events and serious adverse events in 10 placebo-controlled efficacy trials of drugs for hypertension (Benjamin et al., 2008). In this case, they found no difference in the rates of occurrence of such events between the children receiving the placebo and those receiving the study drug.

Some alternatives to the placebo-controlled trial raise their own questions. For example, in noninferiority trials comparing the test drug and an active comparator, one question is, what can be appropriately assumed about the effect of the comparator drug? Randomized withdrawal designs also have disadvantages. The committee discussed issues with this and other trial designs but concluded that a systematic ethical review was not feasible given the complexity of (and disputes about) the issues and the scope of the committee's other tasks.

Ethical Aspects of Pediatric Exclusivity

The committee was not asked to examine the ethical implications of the incentives for pediatric studies provided by BPCA, but these implications, including questions of intergenerational justice, do need attention. It may be argued, on the one hand, that studies conducted in response to the exclusivity incentive for pediatric studies, first, offer justice to the youngest members of society and, second, provide some balance both to usual market forces that favor studies with adults and to federal programs such as Social Security and Medicare. (For a discussion of generational fairness issues and federal policies, see, for example, Newacheck and Benjamin, 2004.) On the other hand, some have cited costs to older members of society associated with the delayed entrance of generic competitors associated with the extra 6 months of marketing protection offered by pediatric exclusivity. For example, Dor and colleagues (2007) noted that although "evidence suggests value in reauthorizing BPCA, significant concerns have been raised over the cost to both the federal government and consumers regarding the length of time (currently 6 months) of the market exclusivity extension" (p. 7). Medicare, Medicaid, and private health insurance plans (and, thus, taxpayers or premium payers) pay some of the costs of higher drug prices, and some are paid by health plan beneficiaries.

Some analyses have attempted to estimate the economic benefit to sponsors of pediatric exclusivity. In an analysis involving nine drugs for hypertension, Baker-Smith and colleagues (2008) reported that the median cost to complete pharmacokinetic studies was $862,000 and that the median cost to complete safety and efficacy trials was $4.3 million. Taking the after-tax sales into account for the 6 months of additional marketing protection, they reported that the ratio of net economic return to study cost was strongly

positive but also quite variable (average return of 17 to 1 with a range from 4 to nearly 65).

In another study that examined nine representative products for which sponsors received exclusivity, Li and colleagues (2007) estimated that the median net benefit from the existing exclusivity period of 6 months was $134,265,456, with a range of a negative $8,946,033 to a positive $507,899,374. (The authors noted limitations of information about the cost to sponsors of conducting trials.) Although generally favorable about the benefits of BPCA, the authors concluded that the pediatric exclusivity incentive of BPCA "overcompensates blockbuster products for performing clinical trials in children while other products have more modest returns on investment under this program" (p. 487).

Both the studies cited above relied on detailed data from sponsor submissions to FDA that are not public (e.g., data on specific lab tests, study site visits, screening of potential participants, and regulatory audits among other variables). For these analyses, FDA allowed investigators who were special government employees to have access to data that were stripped of personal identifiers such as investigator names but otherwise not redacted.

Before the 2007 reauthorization of BPCA, some requested studies led to the granting of pediatric exclusivity without labeling changes and without public access to the clinical and other reviews of the studies. Sponsors obtained the reward of exclusivity with little or no information benefit to clinicians, child patients, or the public. In 2007, Congress sought to correct this situation by requiring that information from studies conducted under BPCA be included in the label and that clinical and other reviews be posted (see Chapter 3). Nonetheless, instances still occur in which sponsors are granted exclusivity without a labeling change (see the discussion of bivalrudin and gatifloxacin in Chapter 7).

Another issue with studies requested under BPCA is the extent to which value can be obtained from a fifth or sixth request for pediatric studies of drugs in the same class and with the same mechanism of action as previously investigated drugs. Because most written requests are not public[7] and because FDA cannot make information about INDs public, it is not possible to identify comprehensively requests that involve the same class of drug, the same indication, all or some of the same types of studies, and all or some of the same age groups.

Multiple studies are a particular concern when they consistently show a lack of efficacy. Chapter 6 describes several such situations with studies with newborns. One question is whether there was a point at which sufficient information showing a lack of efficacy had been submitted that the benefit anticipated from continuing the studies (e.g., data on pharmacokinetics to guide persisting off-label use) no longer justified the risks and economic costs.

CONCLUSIONS

A number of standards are in place to prevent unethical clinical studies in general and with children specifically. They include the FDA and HHS regulations and the

[7] As of February 1, 2012 and required by FDAAA, FDA had posted 47 written requests (with amendments) at http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049997.htm.

system of research review and monitoring that these regulations have helped create; international standards of ethical conduct for pediatric studies; and various programs of ethics education for regulators, investigators, sponsors, and IRBs. The provisions made by Congress for FDA to add expertise in pediatrics and pediatric research ethics offer additional protections to children.

Still, an ethical tension may exist in pediatric drug studies and, indeed, clinical research generally. That is, depending on the specifics of a research situation, investigators in pediatric studies may face a conflict between the best interest of an individual child as a potential research participant and the interests of future children who might benefit from the research. Special safeguards help protect child participants in research, but they do not eliminate the tension. Likewise, although regulations and research ethics programs are valuable, they do not substitute for sponsors, investigators, and FDA staff who—beginning with the earliest stages of study planning through its completion, evaluation, and dissemination—understand and follow ethical and scientific standards for pediatric research.

The committee was not asked to assess the benefits of BPCA and PREA in relation to their costs. Such a policy evaluation would be complicated and require many assumptions in the absence of evidence to support statements about causation. To help provide information for a narrower assessment of the costs incurred and benefits accrued by sponsors of pediatric studies requested under BPCA, Congress or FDA could provide for additional analyses of submissions to FDA (e.g., analyses similar to those cited earlier in this chapter).

Relying primarily on FDA clinical reviews, the committee identified some concerns about pediatric studies conducted under BPCA and PREA. One concern involves placebo-controlled trials. Such trials do not necessarily present problems, but it is important that protocols for such studies be consistent with ethical and scientific standards. The committee suggests that *FDA document the scientific and ethical rationales for the use of placebo-controlled pediatric trials*, first, in written requests that include such studies and, second, in clinical reviews prepared by FDA staff. Such documentation, particularly in cases in which effective alternative treatments exist, could help clarify whether the research will meet or has met the ethical standards described earlier in this chapter. Justification should also be considered in some other situations, for example, when FDA suggests or agrees to the use of an unapproved drug as the active comparator in a controlled trial or to the inclusion of healthy children in pharmacokinetic studies.

Another concern that the committee identified is some continuing limitations on public access to information from studies conducted under BPCA and PREA. Despite substantial improvements for recently submitted studies, access issues continue for clinical and other reviews for older NDA and BLA submissions. Redactions of significant sections of clinical reviews also present concerns.

Congress and FDA have several options to further expand access to information from pediatric studies. *One is for Congress to direct that FDA make public the clinical and other reviews of drugs and biologics approved before September 27, 2007. An additional option is for Congress to direct the Government Accountability Office or other entity independent of FDA to analyze the use of redactions for reviews of pediatric studies*. The task would be to assess whether redactions exceed what is necessary to

protect confidential commercial information and trade secrets and critical aspects of FDA's internal deliberations. A further step would be for *FDA to explore with the National Library of Medicine how clinical and other reviews might be made accessible through PubMed and through links to trials registered at ClinicalTrials.gov.* Such integration could provide an independent assessment to supplement sponsor summaries and publications. *To obtain a better understanding of the dissemination of information, FDA could seek an assessment of private sector dissemination of findings from pediatric studies and labeling changes conducted under BPCA and PREA, including both the speed of dissemination and the accuracy and completeness of the information as disseminated.*

The committee recognizes FDA's limited resources. At the same time, it is concerned that rationales for ethically sensitive decisions be clear and also that the public have access to information in which sponsors, investigators, research participants, taxpayers and premium payers, and FDA staff have already invested—in different ways—considerable expense or effort.

5
Safety and Efficacy Assessments in Studies Conducted Under BPCA and PREA

The goal of the Best Pharmaceuticals for Children Act (BPCA) and the Pediatric Research Equity Act (PREA) is to improve pediatric therapeutics through preclinical and clinical studies of drugs and biologics that are prescribed for children or that have the potential to benefit children. Ideally, such studies lead to the addition of useful information to the labeling of these products and then to the effective dissemination and application of that information to improve clinical care and child health.

BPCA and PREA are components of a complex system for ensuring the drugs for children and adults are safe and effective. The Food and Drug Administration (FDA) and its statutory and regulatory foundations are central elements of this system. As summarized in Chapters 3 and 4, FDA not only assesses and monitors the safety and effectiveness of drugs but also requires protections for adults and children who participate in the trials whose results are submitted for assessment of a drug for approval by the agency. The agency's effectiveness in its multiple roles depends on science-based decision making, credible leadership, committed and well-trained staff, adequate financial resources, and timely and trustworthy communication to professionals and the public (FDA Science Board, 2007; IOM, 2007).

Beyond FDA, the system for ensuring safety and efficacy extends to the organizations and individuals responsible for conducting drug studies and for protecting research participants and research integrity. It thus includes commercial and other sponsors of research, clinical investigators, and institutional review boards (IRBs), as well as health services researchers and others who analyze medication use in clinical practice in an effort to improve the quality, effectiveness, and efficiency of health care. The system also encompasses clinicians who consider available evidence about drug safety and effectiveness as they care for children. Parents have a role, too, including in drug research when they administer test drugs or placebos at home and keep diaries or other records necessary for the assessment of safety and efficacy outcomes.

This chapter discusses selected aspects of FDA's assessments of data on the safety and efficacy of drugs and biologics based on data from pediatric studies requested under BPCA or required under PREA. For safety, these aspects include reviewer conclusions about overall safety signals, risk-benefit assessments, and extrapolation of safety and findings of the 1-year safety reviews first required in BPCA of 2002. For efficacy, the discussion focuses on the use of alternative endpoints and extrapolation.

SOURCES OF INFORMATION ABOUT SAFETY AND EFFICACY RESULTS IN PEDIATRIC DRUG STUDIES

The most comprehensive perspective on the pediatric study data submitted by sponsors and evaluated by FDA is provided in the clinical reviews prepared by staff of the Center for Drug Evaluation and Research (CDER) or the Center for Biologics Evaluation and Research (CBER). For this report, these reviews were the primary source of information on the characteristics and findings of pediatric studies conducted under BPCA or PREA. The committee also consulted clinical pharmacology and statistical reviews (if any), product labeling, and letters describing FDA's approval action and any further requirements (e.g., further pediatric studies). FDA managers may prepare memoranda that provide additional context for decisions or explain why a reviewer's recommendations were not accepted. For some labeling changes, the committee consulted minutes from FDA advisory committee meetings.

Following congressional directives described in Chapters 3, CDER and CBER now post the reviews for products approved on or after September 27, 2007.[1] For products approved earlier, clinical and other reviews are posted for a few products, but the committee had to request that FDA make public the reviews for most products approved before September 2007. (Appendix A describes how the committee selected the sample of requests, studies, and labeling changes assessed in this report.)

As described by CDER, the clinical review (sometimes called the medical review) is a "comprehensive summary and analysis of the clinical data submitted in support of a marketing application . . . [that] also includes the clinical reviewer's assessment of and conclusions about: (1) the evidence of effectiveness and safety under the proposed conditions of use; (2) the adequacy of the directions for use; and (3) recommendations on regulatory action based on the clinical data submitted by an applicant" (CDER, 2010, p. 3). Clinical reviews may summarize findings from other areas of scientific review (e.g., toxicology and microbiology), and reviewers may also cite their own literature searches.

In the years since BPCA and PREA and their predecessor policies went into effect, FDA has improved the organization and completeness of the clinical reviews. In 2004, CDER added to its policy manual a standardized template for clinical reviews, although some reviewers had been using a similar format for some time. Box 5-1 shows the major headings of the CDER template as revised in 2010. (Details of the safety and efficacy sections of the template are presented later in this chapter.) CDER has also created templates for clinical pharmacology and biopharmaceutics reviews and for statistical reviews. In addition, CDER has created a 65-page desk reference guide that provides staff with an accessible resource of principles and procedures (CDER, 2011a). The guide also describes the roles of review team members, including those with specialized expertise (e.g., pediatrics) who may be included as needed.

[1] For CDER and CBER respectively, the reviews for products approved after September 27, 2007 are at http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049872.htm and http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CBER/ucm122938.htm.

BOX 5-1
CDER Template for Clinical Reviews (2010)

1. Recommendations/Risk-Benefit Analysis
2. Introduction and Regulatory Background
3. Ethics and Good Clinical Practices
4. Significant Efficacy/Safety Issues Related to Other Review Disciplines
5. Sources of Clinical Data
6. Review of Efficacy
7. Review of Safety
8. Postmarketing Experience
9. Appendices
   9.1 Literature Review/References
   9.2 Labeling Recommendations
   9.3 Advisory Committee Meeting

SOURCE: *CDER Manual of Policies and Procedures*, 6010.3R (issued December 14, 2010).

As described in the desk reference guide, the primary audience for the clinical review includes the review team (i.e., those with responsibility for various aspects of the overall review), division staff, and CDER managers. The guide notes that reviewers should anticipate "the availability of the document to a public audience" (CDER, 2010, p. A-1).

The Center for Biologics Evaluation and Research (CBER) has not completed work on a standard format for reviews (personal communication, Catherine Lee, Office of Pediatric Therapeutics, FDA, August 8, 2011). Some CBER reviewers have, however, used an outline format similar to that used in CDER reviews. In general, the committee found that CBER reviews were more variable than CDER reviews.

Overall, the committee found that the FDA reviews from recent years tended to be more systematic and focused than earlier reviews. The recent reviews were more likely to highlight key conclusions about safety and efficacy, although they did not invariably follow the template. (Reviews may not follow the template for submissions that involve only pharmacokinetic and limited safety data, as requested by FDA.) Recent reviews also tended to provide more regulatory and other context about the origins and rationales for studies. Occasionally, the reviews summarize interactions between the FDA and sponsors and provide insights into how and why studies changed over time.

ASSESSING AND MONITORING SAFETY IN PEDIATRIC DRUG STUDIES: SELECTED ISSUES

A sponsor's submission of a new drug application (NDA) or biologics license application (BLA) will generally report safety data from preclinical and clinical studies and offer the sponsor's assessments of these data. Submissions may also include data from adult pharmacokinetic and other studies, a review of relevant literature, and postmarket safety reports for already marketed drugs. As noted elsewhere in this report,

almost 10 percent of labeling changes attributed to studies requested under BPCA or required under PREA involved no information from new pediatric studies.

During the course of a clinical trial, the sponsor is responsible for trial monitoring. Depending on the anticipated risks in a trial (usually a Phase III trial), the sponsor may appoint a data monitoring committee (DMC; sometimes called a data safety monitoring board or data and safety monitoring committee) to evaluate safety data as it accumulates.[2] If a DMC identifies serious safety concerns in interim assessments of trial data, it can recommend modification or early termination of a trial. It is the sponsor's responsibility to report serious adverse events and DMC recommendations related to such events to FDA. Unlike the National Institutes of Health (NIH), FDA regulations do not require the appointment of a DMC except in rare circumstances (CDER/CBER/CDRH, 2006). However, CDER's template for written requests includes the option for the agency to require a DMC under other circumstances (CDER, 2011).[3] The Pediatric Review Committee (PeRC, described in Chapter 3) discusses whether a DMC should be required, and FDA may place a clinical hold on a protocol if it concludes that the absence of a DMC puts research participants at unreasonable and significant risk (personal communication, Robert Nelson, Office of Pediatric Therapeutics, FDA, January 16, 2012). An assessment of the use of DMCs in pediatric clinical trials was beyond the task for the committee but may warrant future examination.

CDER Template for Review of Safety in Drug Studies

The CDER template for clinical reviews outlines a comprehensive evaluation and discussion of safety that covers key topics and data sources in a systematic order (Box 5-2). One subsection of the template provides for a discussion (if relevant) of pediatrics and assessment of effects on growth. In practice, reviewers may tailor the format of their assessments to take into account the specifics of a particular submission, for example, whether it presents only a pharmacokinetic and pharmacodynamic study, as requested by FDA. Similarly, although the agency prefers that analyses pool data across studies, some sponsor submissions may not support this strategy.

BOX 5-2
Safety Review Section of CDER Clinical Review Template (2010)

Safety Summary
Methods
  Studies/Clinical Trials Used to Evaluate Safety

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[2] As described in FDA guidance, a DMC is "a group of individuals with pertinent expertise that reviews on a regular basis accumulating data from one or more ongoing clinical trials. The DMC advises the sponsor regarding the continuing safety of trial subjects and those yet to be recruited to the trial, as well as the continuing validity and scientific merit of the trial" (CDER/CBER/CDRH, 2006, p. 1).

[3] For example, in 2005, FDA requested a study of griseofulvin (an off-patent drug approved for treatment of tinea capitis in children 2 years of age or older) to provide more data on pharmacokinetics, safety, and efficacy related to different dosing recommendations. FDA stated that a "Data Monitoring Committee with pertinent expertise must be used to provide ongoing oversight of patient safety" (Beitz, 2005, p. 4).

- Categorization of Adverse Events
- Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

Adequacy of Safety Assessments
- Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations
- Explorations for Dose Response
- Special Animal and/or In Vitro Testing
- Routine Clinical Testing
- Metabolic, Clearance, and Interaction Workup
- Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Major Safety Results
- Deaths
- Nonfatal Serious Adverse Events
- Dropouts and/or Discontinuations
- Significant Adverse Events
- Submission-Specific Primary Safety Concerns

Supportive Safety Results
- Common Adverse Events
- Laboratory Findings
- Vital Signs
- Electrocardiograms (ECGs)
- Special Safety Studies/Clinical Trials
- Immunogenicity

Other Safety Explorations
- Dose Dependency for Adverse Events
- Time Dependency for Adverse Events
- Drug-Demographic Interactions
- Drug-Disease Interactions
- Drug-Drug Interactions

Additional Safety Explorations
- Human Carcinogenicity
- Human Reproduction and Pregnancy Data
- Pediatrics and Assessment of Effects on Growth
- Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Additional Submissions/Safety Issues

SOURCE: *CDER Manual of Policies and Procedures* (Section 7 of Clinical Review Template), 6010.3R (issued December 14, 2010)

New Rules to Improve Reporting of Adverse Events and Analysis of Safety Data from Clinical Trials

Central to the assessment of drug safety are the identification and evaluation of adverse events both during clinical trials and after marketing approval. FDA regulations define an adverse event as "any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related" (21 CFR 312.32(a)). Such an event can involve, for example, a laboratory or other test result, a symptom, a hospitalization, or a death. An adverse reaction is an adverse event that is attributed to use of the drug.

In 2010, FDA issued new regulations and guidance on safety reporting for clinical trials (CBER/CDER, 2010a). The goal was to "increase the interpretability of and usefulness of safety data available to the clinical investigators, IRBs, and the FDA" (Sherman et al., 2011, p. 5). The rules require clinical investigators to report all serious adverse events to trial sponsors. They shift the responsibility for assessing whether an isolated adverse event is likely to be drug related from individual investigators to sponsors. As a result, sponsors should have a larger and more complete pool of data to support assessments of causality. These assessments should improve the relevance of their reports to FDA.

The 2010 rules also offered several examples of the kinds of events on which sponsors should focus. They include the following:

- A single occurrence of an event that is uncommon and known to be strongly associated with drug exposure (e.g., angioedema, hepatic injury, and Stevens-Johnson syndrome);
- One or more occurrences of an event that is not commonly associated with drug exposure but that is otherwise uncommon in the population exposed to the drug (e.g., tendon rupture); and
- An aggregate analysis of specific events observed in a clinical trial (such as known consequences of the underlying disease or condition under investigation or other events that commonly occur in the study population independent of drug therapy) that indicates that those events occur more frequently in the drug treatment group than in a concurrent or historical control group. (CDER/CBER, 2010b, p. 4)

IOM Review of Safety Assessments in Pediatric Drug Studies

As explained in Chapter 1, the Institute of Medicine (IOM) was asked to assess "the number and type of pediatric adverse events" in a sample of studies conducted under PREA or precursor regulations. The committee also included a sample of studies stemming from requests under BPCA. This broader scope provided additional context for understanding FDA's evaluation of safety findings in pediatric drug studies.

Unfortunately, the FDA clinical reviews examined by the committee were completed before FDA's shift to the new, more targeted strategy for reporting adverse events. The typical clinical review included numerous, sometimes lengthy tables and reports of various categories of adverse events that correspond to topics in the review template. The reviews focused on serious and unexpected adverse events reported in clinical trials, but they also discussed less serious events. The sponsor and FDA reviewers judged many adverse events described in the clinical reviews not to be related to the test product.

Given the thoroughness of most reviews and the usual judgment that a substantial proportion of reported adverse events were not related to the test drug, the IOM committee decided that it would not be productive to review and assess the numbers and types of these events. Instead of counting and categorizing individual adverse events, the committee focused on the clinical reviewer's more general and relevant conclusions

about a product's safety profile. For example, for products that had been studied in adults, did the FDA reviewer conclude that pediatric studies of a drug or biologic showed a safety profile that was similar to that reported for adults? Alternatively, did the profile for children differ from that for adults in ways that, at a minimum, warranted discussion in the product's labeling? If the FDA reviewer did not compare pediatric safety findings to adult safety findings, did he or she make other appropriate comparisons (e.g., with findings for a control group or with safety findings in other pediatric studies of similar drugs for the same condition)?

Because safety is relative, FDA must weigh findings about the risks of a product against expected benefits and judge whether the expected benefits sufficiently outweigh expected harms to justify approval for marketing. (FDA may disapprove the labeling of a product for pediatric use but provide for the addition of safety or other information from pediatric studies to the product labeling for already marketed products.) In assessing clinical reviews, the committee looked for a risk-benefit assessment (to use FDA's language), that is, an explicit overall judgment about risks in relation to expected benefits. In some cases, the committee found that a reviewer's discussion of the risk-benefit assessment was redacted without explanation. A memo from a division director or review team leader sometimes indicated that agency management reached different conclusions from the primary reviewer.

The committee initially intended to assess the extent labeling changes were consistent with the reviewer's conclusions about safety signals or significant adverse events. However, after discovering that FDA generally redacted all or much of the discussion of labeling in clinical reviews, the committee decided that it could not be confident in making such assessments. As discussed in Chapter 3, the sponsor owns the label, and new labeling or changes in labeling usually result from a process involving negotiation between the sponsor and FDA about the sponsor's proposed wording.

Analysis of Safety Profile

For products that had also been studied in adults, most clinical reviews that the committee examined offered relatively straightforward and easily understood conclusions about whether the safety findings from pediatric studies showed results similar to those found from adult studies. The majority of the reviews that included comparisons of the results for children with the results for adults (or with the known safety profile of the product) concluded that the safety profile was similar for children. For example, in the assessment of leflunomide (Arava) for the treatment of juvenile rheumatoid arthritis, the reviewer's summary conclusion was that the "overall profile of adverse events was consistent with the underlying disease and known serious adverse events of leflunomide" (Yancey, 2003, p. 68). The summary also notes hepatotoxicity to be a known risk of the drug. To cite another example, the clinical reviewer for tenofovir disoproxil fumarate (Viread) noted that "[o]verall, the safety issues identified in the adolescent study are similar to those previously identified in the adult clinical trials and are included in the current product label" (Levorson, 2010, p. 40). The reviewer then described several specific safety issues, including reductions in bone mass density, renal toxicity, and gastrointestinal events. For one product (eletriptan hydrobromide [Relpax]), the

labeling—but not the redacted clinical review—stated that the profile of adverse events in a pediatric study was similar to that reported in studies with adults.

Because one objective of FDA's evaluation of adverse events in pediatric studies is to determine whether a product's labeling needs to be revised, reviewers sometimes explicitly noted whether the findings about treatment-related adverse events in children were reflected in the existing labeling (for previously approved products) or whether some revisions were needed. As noted earlier, reviewers' specific discussions of the text of proposed labeling were mostly or entirely redacted.

For some products, reviewers found different safety signals, usually in the form of events that, although expected, were more common in children than in adults. In a few instances, the findings were unexpected on the basis of the data for adults. Box 5-3 provides examples of these kinds of reports.

BOX 5-3
Examples of Products with Different Safety Profiles for Children and Adults Identified in FDA Clinical Reviews

Adalimumab (Humira) for treatment of juvenile idiopathic arthritis. "Safety was similar to that seen in adults but there were several safety signals not observed in the adults, including elevations of creatine phosphokinase (CPK). In addition, a higher rate of immunogenicity was observed in children as compared to adults as well as a higher rate of non-serious hypersensitivity reactions. There was disagreement between the primary clinical reviewer and the secondary reviewer on the specific details of the post-marketing registry that should be conducted" (Siegel, 2008b, p. 3).

Aripiprazole (Abilify) for treatment of schizophrenia. "Based on a comparison of the results of five short-term adult studies in schizophrenia with the results of this pediatric schizophrenia study, the safety profile of aripiprazole in adolescents with the diagnosis of schizophrenia is comparable to the adult schizophrenia population, with the exception of dose-related occurrence of higher frequency of somnolence and extrapyramidal symptoms observed in the pediatric population" (Zhang, 2007, p. 35).

Desflurane (Suprane) for induction or maintenance of anesthesia. "The clinical data submitted in this supplement demonstrated a marked increase in the incidence of both major (associated with significant oxygen desaturation) and minor respiratory events including laryngospasm, airway obstruction, secretions, and breath holding in non-intubated pediatric patients who underwent maintenance anesthesia with desflurane compared to a cohort of children treated similarly with isoflurane. The incidence of these respiratory events appeared to be related to the inspired concentration of desflurane. These data do not support the use of desflurane for induction (which was a prior finding) or maintenance of anesthesia in non-intubated children" (Shibuya, 2006, p. 4).

Olmesartan (Benicar) for treatment of hypertension. "In this whole study program, transient minor to moderate headache was the major adverse event with this product in pediatric population. Other than that, there does not appear to be any other unexpected adverse events in children compared to adults" (Xiao, 2009, p. 10).

Omalizumab (Xolair) for treatment of asthma. "[I]n patients 6–11 years of age with IgE [immunoglobulin E] levels above 500 IU/mL, circulating trough levels of omalizumab and

omalizumab-IgE complexes are higher than those achieved in patients 12 years of age and older with IgE levels up to 700 IU/mL. These complexes take months to clear after termination of Xolair treatment. Although no urinary abnormalities or evidence of serum sickness was noted in the safety database, the clinical meaning of higher circulating immune complex exposure, particularly over many years of chronic exposure, is unknown. Thus, lack of evidence supporting the long-term safety of a dosing regimen associated with circulating immune complex levels that are higher in children higher [*sic*] than those studied and approved in adults is a safety concern with this application" (Starke, 2009, p. 12).

Some drugs were studied in populations and for indications that did not lend themselves to comparisons with the findings of studies with adults. An example is nitric oxide (INOmax) for the treatment of neonates with bronchopulmonary dysplasia, a condition not diagnosed in adults. Even when comparisons with adult safety findings were possible, some reviewers chose to make other informative comparisons. To cite an example, in the clinical review of a combination salmeterol xinafoate and fluticasone propionate product (Advair Diskus), the comparison was with the safety profiles for the individual components of the product, which were similar to those for the combination product (Johnson, 2000). For some products, the comparison was with previously studied products or formulations. In the review of mometasone furoate (Asmanex) for treatment of asthma, for example, the reviewer noted that the adverse events identified were common and consistent with those found in other trials of similar drugs in pediatric patients "and do not suggest a new safety signal" (Karimi-Shah, 2007, p. 11).

In reaching overall conclusions about safety, some reviewers did not make comparisons with other populations or products. For example, the reviewer for alendronate (Fosamax) for osteogenesis imperfecta stated that "the safety and tolerability profile of alendronate in this population were acceptable, with few serious adverse events (only three of which were possibly related to alendronate) and no deaths" (Schneider, 2003, p. 3). The reviewer also noted one case of leukopenia—a condition not identified to be a risk for adults—and suggested that that this type of event be monitored as a safety issue, regardless of whether FDA approved the drug for treatment of the studied indication.

Some reviews stated only that no unexpected adverse events had been noted. In context, such statements probably can be interpreted as suggesting that the safety profile was similar to that for adults if the product had been previously studied in adults. For example, in an assessment of irinotecan hydrochloride (Camptosar) for refractory solid tumors, a clinical reviewer concluded that the pediatric studies provided no meaningful new safety information (Ibrihim, 2003).

Although reviewers differed in how they summarized and presented the information, the reviews typically supplemented the overall assessment of safety with a summary of serious adverse events that are considered to be related to the drug and a summary of common treatment-related adverse events. One example of a clear, relatively brief summary of such adverse events is provided in the clinical review of a sponsor submission involving almotriptan (Axert) for the treatment of migraine in adolescents (Harris, 2009). In three short paragraphs, the reviewer notes that 67 percent of the study participants had some kind of adverse event (all causality), that 8 percent had an adverse event that was judged to be related to the product, that these events were most often

nausea and somnolence (each reported by 1.4 percent of participants), and that 2 percent of participants experienced a serious adverse event, none of which was judged to be treatment related.

Risk-Benefit Assessment

Explicit statements of risks in relation to benefits usefully underscore the reality that the use of drugs involves the potential for harm as well as for benefit. Few (7 of 46) of the clinical reviews in the committee's sample included fairly explicit summary risk-benefit statements.[4] An example of an explicit positive assessment is found in the review of tenofovir disoproxil fumarate (TDF; Viread): "The identification of the same potential safety risks in adolescents as in adults on TDF did not outweigh the benefit of TDF as a treatment option for either treatment-experienced or treatment-naïve, HIV-infected patients with HIV-1 virus sensitive to TDF" (Levorson, 2010, p. 8). All explicit statements were in reviews dated 2008 or later.

Most reviews (32 of 46) included no direct statement about the risk-benefit balance. Some of these reviews, however, organized clear but separate summary statements about efficacy and safety close enough in proximity that the overall judgment about the balance was reasonably evident.

FDA reviewers occasionally conclude that study results are not interpretable. For example, in the case of sotalol hydrochloride (Betapace) for arrhythmia, FDA had issued a written request for pharmacokinetic and pharmacodynamic data to guide use of the drug in prepubertal children. Although the FDA reviewer reached some conclusions about dosing, the overall conclusion was that neither the requested studies nor the other pediatric data submitted could "be interpreted with respect to establishing either the safety or the efficacy of sotalol in the pediatric population" (Karkowsky, 2000, p. 3). (See also the entry for etodolac [Lodine] in Box 7-3.)

Two reviews (for esomeprazole magnesium [Nexium] and gatifloxacin ophthalmic [Zymar]) were not classified because the risk-benefit section of the review was significantly redacted. In another review (for omalizumab injection [Xolair]), most of the discussion in the risk-benefit section was redacted, but the review later included this explicit information: "[the Pulmonary-Allergy] Advisory Committee voted against (4 yes, 10 no, 0 abstain) the risk/benefit favoring approval of Xolair, i.e., whether the safety and efficacy data provide substantial and convincing evidence to support approval of

[4] Sorting out risk-benefit assessments could be complicated. One clinical pharmacology review of guanfacin (Intuniv) for attention deficit-hyperactivity disorder was explicit but mixed. "The drug has not demonstrated additional benefit over placebo in patients who are 13 years or older (who tend to be heavier), the risk outweighs the benefit in this age group. In patients who are 6-12 years of age, the benefit-risk ratio is probably greater than unity" (Mishina, 2007, p. 17). The clinical reviewer was, however, implicitly positive; the product was labeled for use in both age groups, as explained in the division director's memo. "An age analysis clearly suggests that the benefits of SPD503 were not demonstrated in adolescents, even though the studies were positive overall. I still think it is reasonable to permit a general claim of efficacy in this broad age range (6-17), along with a mention of this finding in labeling. With mg/kg dosing, I think adolescent patients can be effectively treated. The sponsor's proposed explanation based on likely inadequate exposure due to higher body weights in adolescents seems entirely reasonable to me. The sponsor has agreed to address this discrepancy in the efficacy findings as a phase 4 commitment. The sponsor has also committed to conducting a maintenance study post-approval" (Laughren, 2009c, p. 3).

Xolair in this age group" (Starke, 2009, p. 96).[5] Three reviews involved submissions that did not include efficacy studies.

The reviews that the committee examined did not explain or cite any underlying methodology for weighing safety and efficacy findings. A 2007 IOM report on FDA's drug safety system noted that "the risk-benefit analysis that currently goes into regulatory decisions appears to be ad hoc, informal, and qualitative" and recommended that FDA "develop and continually improve a systematic approach" to such analyses (IOM, 2007, pp. 123 and 125). In a 2009 summary of responses to that report, the agency reported that it was continuing to explore best practices in risk-benefit assessments, including identifying and developing the information technology and analytic infrastructure to support such assessments (FDA, 2009c). In 2010, FDA announced that in early 2013 it intended to publish for comment a structured benefit-risk assessment framework (FDA, 2010c). A framework based on sound regulatory science could make an important contribution to FDA's assessments of pediatric drug studies.

Extrapolation of Safety

As discussed later in this chapter, the Food and Drug Administration Amendments Act of 2007 (FDAAA; PL 110-85) and earlier laws and regulations permit the extrapolation of "pediatric effectiveness" on the basis of data from studies with adults (or data from studies with another pediatric age group), usually with additional supplementary information on pharmacokinetics and safety. The extrapolation of safety is not mentioned. In discussions with the committee and staff, FDA representatives said that the agency generally does not accept the extrapolation of safety.

Arguably, the agency does, in some cases, allow the extrapolation of safety. For example, for pancrelipase (Creon), which is used to treat exocrine pancreatic insufficiency due to cystic fibrosis or other conditions, the Pediatric Review Committee (PeRC) made the following recommendation:

> On consideration of available information, including studies of the TbMP [to-be-marketed product] in patients with CF [cystic fibrosis]-related EPI [exocrine pancreatic insufficiency] 12 years and older, an extensive literature base describing a favorable risk:benefit balance for long-term use of non-TBMP PEPs [pancreatic enzyme replacement products] in adult and pediatric patients with CF- and chronic pancreatitis-related EPI, and widely implemented dose guidelines (the Cystic Fibrosis Foundation Guidelines) for patients with CF-related EPI based on studies performed with other PEPs, the Pediatric Review Committee (PeRC) recommended to the Division of Gastroenterology Products (DGP) that *safety and*

[5] The review, which was categorized as providing an explicit assessment, also noted that the majority of the committee held that safety had not been adequately investigated and that the group split evenly on the evidence of efficacy. On efficacy, those who expressed concerns believed that the drug had not been studied in the patients for whom it was intended (pediatric study subjects had normal results for tests of forced expiratory volume in 1 second [FEV1] tests, whereas adults had severe asthma that was not responsive to other treatments). On safety, one of the primary concerns was "the lack of dose ranging," particularly the option of a lower dose (p. 95).

> *efficacy in children could be extrapolated* to include an indication to treat EPI in children of all ages. (Ku and Hausman, 2009) [emphasis added]

For another product, antihemophilic factor (recombinant) FS (Kogenate), the approval letter stated that the pediatric study requirements had been fulfilled for all age groups (Golding, 2008b). The clinical reviewer, who assessed data submitted for children ages birth up to 2.5 years, stated that PeRC had recommended that the study requirements be considered completed rather than be waived and had judged that the benefits of prophylactic treatment could be "extended to all pediatric age groups provided the patient presents with no existing joint damage" (Jain, 2008, p. 2). The review cited no pharmacokinetic or safety studies for older children and thus implies the extrapolation of safety as well as efficacy. Approvals of contraceptives for use by women past the age of menarche but under age 18 years are routinely granted on the basis of findings from efficacy and safety studies with adult women with no product-specific safety or other studies for younger women (see, e.g., Beitz, 2010).

Extrapolation of safety as well as efficacy for a particular product may be appropriate in special circumstances. In these circumstances, it would be informative for FDA to provide the public with an explicit justification for such extrapolation. If the agency's position is that decisions such as those just cited do not involve the extrapolation of safety, then it would likewise be desirable for the rationale for this stance to be made clear.

Long-Term or Other Studies or Safety Reporting After a Pediatric Labeling Change

As it reviewed the safety findings in its sample, the committee identified concerns about long-term product-related adverse events—including neurological and growth-related events—that would not be evident in the submitted studies. As discussed in Chapter 2, results of medication use in actual practice may differ from results in carefully controlled clinical trials that involve selected populations and strict protocols for product use and monitoring. Results may, in particular, differ for products that have been labeled on the basis of short-term studies but that are used on a long-term basis—potentially over a decades-long life span in children—for the treatment of chronic conditions, such as asthma or diabetes. Even when use is more limited (days, weeks, or months), long-term neurological and other consequences may be a worry for certain products.

Congress and FDA clearly recognize the problem and have taken some steps to address it. The 1-year safety reviews described below provide examples specific to products with labeling changes resulting from studies conducted under BPCA or PREA. In addition, the recent expansion of FDA's authority to require (non-PREA) studies after marketing approval offers potential safeguards for both children and adults. (See Chapter 3 for further discussion of this authority as well as the Adverse Event Reporting System.)

FDA may also support selective research to assess safety risks to children. For example, the Agency for Healthcare Research and Quality (AHRQ) and FDA recently supported a retrospective cohort study to assess cardiovascular risks of drugs used to treat attention deficit-hyperactivity disorder (ADHD). Using data from four U.S. health plans,

investigators concluded that the data did not suggest a significant risk of serious cardiovascular events in children or young adults using one of several different classes of drugs for ADHD or using methylphenidate specifically (Cooper et al., 2011). The mean duration of follow-up ranged from 1.5 to 3.9 years. Pharmacoepidemiologic studies of this and other kinds can expand the understanding of long-term safety outcomes.

One-Year Safety Reviews

As a partial response to concerns about long-term safety, Congress now requires the Pediatric Advisory Committee (PAC) to evaluate safety information reported in the year following a labeling change resulting from studies conducted under BPCA or PREA. Such reviews were first required in 2002 for products studied under BPCA. In 2007, Congress extended the review to products studied under PREA. FDA posts the slides for the staff presentations to the advisory committee. These presentations not only may provide information about adverse events (from the Adverse Event Report System database described in Chapter 3) but may also offer brief synopses of the original trials and labeling, any subsequent changes in the safety labeling, and trends in pediatric and adult use. Presentations are abbreviated for products that are not being marketed in the United States, that are not widely used by children, or for which few or no pediatric deaths or serious adverse events have been reported (Murphy, 2011).

Table 5-1 summarizes the results of the 1-year safety reviews. Of the 147 products considered from the initiation of the review process in 2003 through June 2011, 100 stemmed from BPCA-related actions (dating from 2002) and the rest stemmed from PREA-related actions (dating from 2007).

TABLE 5-1 Summary of PAC Recommendations from the Safety Review 1 Year After a Labeling Change Resulting from a Study Conducted Under BPCA or PREA, June 1, 2003, to June 30, 2011

Number of Actions	Type of Action
98	Recommended return to routine review
7	Requested additional information and then recommended return to routine review
8	Requested further review; follow-up has not yet been reported
16	Recommended labeling change and labeling change made
10	Recommended labeling change and labeling change not yet made
10	Recommended other actions for specific drug classes (e.g., proton pump inhibitors and antipsychotics)
11	Recommended other actions

NOTE: N = 160, excluding one product not marketed in the United States.
SOURCE: Compiled from safety reporting information posted at http://www.fda.gov/ScienceResearch/SpecialTopics/PediatricTherapeuticsResearch/ucm123229.htm.

Following the presentation of the 1-year safety reports to PAC, the most common recommendation (61 percent of reviews) has been for a return to routine safety monitoring. Of the 36 recommendations for labeling changes, 16 revisions had occurred as of June 2011; other labeling changes may be made in the future.

The posted summaries of PAC meetings have reported extensive discussions over certain classes of products, including selective serotonin reuptake inhibitors, proton pump inhibitors, and atypical antipsychotics. In September 2011, for example, FDA provided an update on a study to further investigate concerns about pediatric use of second-generation antipsychotics and metabolic effects (Gerhard, 2011). The study (undertaken in collaboration with AHRQ) looked specifically at the risk of type 2 diabetes.

Required Postmarketing Safety Studies

As described in Chapter 3, in approving an NDA or BLA, FDA may require sponsors to undertake additional studies beyond those required under PREA. In its sample of 45 labeling changes, the committee found that nine approval letters included postmarket study requirements not required under PREA. The required studies included

- an analysis of already collected data (for salmeterol xinafoate and fluticasone propionate [Advair], a summary of existing pharmacokinetic and pharmacodynamic data for possible gender effects of the drug, with clinical study to be undertaken if this summary was inadequate to identify such effects [Meyer, 2000]);
- a study in animals (for almotriptan [Axert], a toxicology study in juvenile rats to identify unexpected and serious adverse effects on postnatal growth and development [Katz, 2009]);
- a carcinogenicity study (for hydrocortisone butyrate [Locoid lotion], a 2-year dermal carcinogenicity study [Kukich and Walker, 2007]);
- a controlled trial to examine effects on bone mineral density (for tenofovir disoproxil fumarate [Viread] [Birnkrant, 2010b]); and
- a 10-year observational study (for the use of adalimumab [Humira] in 800 pediatric patients with polyarticular juvenile idiopathic arthritis [Roca, 2008]).

The long-term observational study cited above was the only such study in the committee's sample, although the committee is aware of a similar study design requirement for at least one other study. In that case, when FDA approved pegylated interferon alfa 2b (PegIntron) in combination with ribavirin (Rebetol) for treatment of chronic hepatitis C virus in children ages 3 to 17 years, it required the completion of a 5-year follow-up observational study to assess the durability of the treatment response, long-term or delayed toxicity, and long-term effects on height and weight (Birnkant, 2008a).

FDA may also encourage rather than require follow-up studies. For example, in approving a supplemental NDA to add information from requested studies of the anticancer drug irinotecan hydrochloride (Camptosar), FDA recommended but did not require a follow-up pharmacokinetic study to characterize the exposure toxicity relationship for the drug (Pazdur, 2004). Similarly, written requests under BPCA may

encourage but not require long-term studies. For example, for studies of aripiprazole (Abilify) for pediatric schizophrenia and mania in biopolar disorder, the written request identified the effects of the drug on growth and development to be an important concern, but FDA only "encourage[d]" the sponsor "to consider longer-term studies of a year or more to address this question if the acute studies demonstrate efficacy" (Behrman, 2003, p. 5). The submitted studies involved a 6-week placebo-controlled trial for each indication and a 6-month, open-label, follow-on study that included children from either of the controlled studies.

ASSESSING AND REPORTING EFFICACY IN PEDIATRIC DRUG STUDIES: SELECTED ISSUES

Efficacy refers to the achievement of desired results in controlled clinical studies. In its statement of task, IOM was specifically asked to assess the use of alternative endpoints and the use of extrapolation for pediatric subpopulations, both of which are relevant to assessments of efficacy in pediatric drug studies. As was the case for the assessments of safety, the committee primarily relied on FDA clinical reviews for these assessments of efficacy.

Not all studies requested under BPCA or required under PREA specify that studies of efficacy be performed or that determinations of efficacy be a primary objective. For example, when the FDA issued a written request for the controlled study of desflurane (Suprane), the primary objective was to evaluate the safety of the product for the maintenance of anesthesia in nonintubated children (Jenkins, 2001).[6] Likewise, some of the neonatal studies discussed in Chapter 6 specified pharmacokinetic and safety studies but not efficacy studies.

CDER Template for Review of Efficacy in Drug Studies

Box 5-4 presents the efficacy review section of CDER's clinical review template. As is the case for the safety review, this section of a review may include a discussion of sponsor- or reviewer-conducted literature searches and may also cite findings from clinical trials involving adults, in addition to results from trials involving children. The introduction, particularly for recent reviews, usually includes a concise summary of the reviewer's conclusions about efficacy.

[6] The original request specified two studies: one with children ages 2 to 16 years and a second one with children ages 1 month up to 2 years that was to be conducted depending on the findings of the safety analysis conducted in the first study. After the first study raised safety concerns, the second study was dropped in an amended written request (without explicit mention or explanation) (Meyer, 2006).

BOX 5-4
Efficacy Review Section of CDER Clinical Review Template

Efficacy Summary
Indication
- Methods
- Demographics
- Subject Disposition
- Analysis of Primary Endpoint(s)
- Analysis of Secondary Endpoint(s)
- Other Endpoints
- Subpopulations
- Analysis of Clinical Information Relevant to Dosing Recommendations
- Discussion of Persistence of Efficacy and/or Tolerance Effects
- Additional Efficacy Issues/Analyses

SOURCE: *CDER Manual of Policies and Procedures* (Section 6 of Clinical Review Template), 6010.3R (issued December 14, 2010).

The guidance for use of the template advises that "[c]onsultation with the biostatistical reviewer is invaluable when formulating the review of efficacy" (CDER, 2010, p. A-15). Most but not all clinical reviews of efficacy are accompanied by a statistical review. A statistical review may not be prepared for a variety of reasons, for example, if a study of safety and efficacy enrolls too few children to allow any definitive conclusions about efficacy.

Use of Alternative Endpoints

Definition and Rationales for Use of Alternative Endpoints

For the purposes of this report, alternative endpoints in pediatric studies are defined to be measures of efficacy that take pediatric development into account and thus differ from endpoints that were used in adult studies for the condition being investigated. For example, a measure of pain based on a parent's assessment of a young child's physical movements or facial expressions is an alternative endpoint if studies with adults relied on direct self-reporting by the research participant. If multiple primary efficacy endpoints are specified for pediatric studies, one endpoint may the same as that used in studies with adults and another may be an alternative endpoint. In addition, if separate efficacy studies with individuals in different age groups are included in the same NDA or BLA, the efficacy endpoints may vary for older and younger age groups.

For a condition that is found solely in children, the pediatric endpoint may be unique. For example, bronchopulmonary dysplasia is a lung disease of neonates that may occur in premature infants who require mechanical ventilation. Thus, a clinical trial endpoint based on the frequency of the condition in ventilated infants after treatment with

a test drug or placebo cannot be characterized as an alternative to an endpoint for an adult study. For conditions such as attention deficit hyperactivity disorder and irritability associated with autism that may be first identified and studied with children but are subsequently diagnosed in adults, efficacy endpoints for pediatric drug studies are not considered alternative if they are defined prior to studies with adults.

An alternative endpoint may also be a surrogate endpoint, that is, an endpoint such as bone mass density that is used in place of an endpoint or outcome that is more directly meaningful to patients, such as a bone fracture.[7] In studies of drugs to treat osteoporosis in adults, the rate of fractures is the primary efficacy measure. In pediatric studies of the same drugs to treat low bone mass in osteogenesis imperfecta, FDA has specified change in bone density (a surrogate measure) to be the primary endpoint; fracture rate is one of several secondary endpoints (see, e.g., Schneider, 2003). (In studies focusing on prevention rather than the treatment of osteoporosis in adults, a bone density measure has been a primary endpoint.)

Consultants from CDER's Study Endpoint and Labeling Development Group may be involved in consultations about pediatric endpoints without being cited in clinical reviews. The group is also involved in the process that FDA created to evaluate and qualify biomarkers, patient-reported outcome tools, and other measures that sponsors may use in specific drug development efforts so that the appropriateness of each such use does not have to be individually evaluated (CDER, 2010).

In addition, FDA may support analyses of alternative or other endpoints in various contexts. For example, in the context of a advisory committee discussion of modifications to a 2001 written request for the study of sildenafil (Revatio) for the treatment of pediatric hypertension, a staff member from CDER's Office of Biopharmacometrics discussed data on the use of a hemodynamic measure (the pulmonary vascular resistance index) as an alternative to the 6-minute walk test used for adults (Brar, 2010; CRDAC, 2010).

As noted in Chapter 2, alternative endpoints may be used in pediatric studies in several circumstances. These include when

- the use of the adult endpoint is impossible, for example, when that endpoint depends on a pulmonary function test that cannot be reliably performed by young children or when it requires self-reporting of symptoms and the children to be studied are preverbal;
- the use of the adult endpoint is too risky given the circumstances, for example, when a measurement process used only for research purposes (such as an evaluation by magnetic resonance imaging that has no prospect of benefit) requires a research participant to remain still and would require sedation for children in the age group to be studied;
- the condition being studied has somewhat different manifestations in children (e.g., juvenile rheumatoid arthritis versus adult rheumatoid arthritis);

[7] As defined elsewhere by an NIH working group, a surrogate measure is a "biomarker that is intended to substitute for a clinical endpoint. A surrogate endpoint is expected to predict clinical benefit (or harm or lack of benefit or harm) based on epidemiologic, therapeutic, pathophysiologic, or other scientific evidence" (Biomarkers Definitions Working Group, 2001, p. 91).

- the adult endpoint involves measures of common social interactions or functioning (e.g., at work) that do not reflect children's situations; and
- a before-and-after treatment measure could be affected by children's development as well as treatment-related change (e.g., change in bone mass density).

Results of Committee Assessments

The clinical and other reviews and the written requests that the committee examined usually did not note whether the endpoints used for pediatric studies were different from the endpoints used for adult studies. They likewise typically did not discuss the rationale for the endpoints. In some cases, the committee consulted descriptions of studies with adults to determine whether different endpoints were used in the pediatric studies.

For the sample of requested or required pediatric studies and labeling changes that the committee examined, almost half (23 of 49) used primary efficacy endpoints that were the same as those used in adult studies. Roughly one-fifth (11 of 49) involved alternative endpoints. For one product for which two primary endpoints were specified, one of the endpoints was also used in studies with adults and the other was an alternative endpoint. In most of the remaining cases, the studied indications were primarily or entirely found in the pediatric population (seven cases) or primary efficacy endpoints were not required or requested (six cases). Three of the 49 product assessments involved efficacy studies that had different primary efficacy endpoints for different age groups. For one efficacy study (for moxifloxacin ophthalmic [Vigamox] for the treatment of bacterial conjunctivitis in neonates), the section of the clinical review that presumably described the endpoint and results was redacted.

Box 5-5 presents examples of the different categories of endpoints reported in the clinical reviews that the committee examined. More than one indication could be evaluated for a single product, or different efficacy endpoints could be used for different age groups.

BOX 5-5
Examples of Efficacy Endpoints in Pediatric Studies

Alternative Endpoint

Adalimumab (Humira)

Indication: juvenile rheumatoid arthritis

Primary efficacy endpoint: disease flare measured by a 30 percent worsening in at least three of six juvenile rheumatoid arthritis core set criteria and a minimum of two active joints AND 30 percent improvement in not more than of six juvenile rheumatoid arthritis core set criteria specified by American College of Rheumatology (Siegel, 2008b)

Alendronate (Fosamax)

Indication: osteogenesis imperfecta

Primary efficacy endpoint: change in lumbar spine bone mass density (BMD) *Z*-score (standard deviations from the mean for age-matched healthy controls) from baseline (Schneider, 2003)

Buspirone hydrochloride (Buspar)

Indication: generalized anxiety disorder (ages 6 up to 17 years)
Primary efficacy endpoint: change from baseline in the sum of four scores from C KSADS GAD (Columbia Kiddie Schedule for Affective Disorders and Schizophrenia–General Anxiety Disorder scale) that are specific to anxiety (Laughren, 2000)

Endpoint Also Used in Adult Studies
Aripiprazole (Abilify)
Indication: schizophrenia (ages 13 up to 17 years)
Primary efficacy endpoint: Positive and Negative Syndrome Scale (Zhang, 2007)
Hydrocortisone butyrate (Locoid)
Indication studied: atopic dermatitis (ages 3 months or older)
Primary efficacy endpoint: Physician's Global Assessment score (Katz, 2007)

Other (Primarily or Entirely a Pediatric Condition)
Methylphenidate (Concerta)
Indication studied: attention deficit-hyperactivity disorder (ages 6 up to 12 years)
Primary efficacy endpoint: IOWA Conners Teacher Rating Scale (Inattention/Overactivity Subscale) (Mosholder, 2000a)

For the most part, FDA reviewers did not raise concerns about the use of alternative endpoints as such. Some reviewers noted that the endpoints were based on measures validated for the indication and age group studied (see, e.g., Siegel, 2008b). In general, it would be desirable for specification of alternative endpoints to be accompanied by some discussion of evidence supporting their reliability and validity.

For several studies of asthma drugs, the committee had concerns about the endpoint specified for studies in children ages 4 to 11 years. The endpoint, forced expiratory volume in 1 second (FEV1), is widely accepted for use with adults and older children, but it requires physical maneuvers that children under age 6 years cannot reliably perform (see Chapter 2). As a result, for levalbuterol hydrochloride [Xopenex inhalation] for the treatment of asthma, FDA approved labeling for use only in the age group 6 to 11 years old, even though the requested study was supposed to assess drug safety and efficacy in the age group 4 to 11 years old. Three other products (albuterol sulfate [Ventolin HFA], levalbuterol tartrate [Xopenex HFA], and salmeterol xinafoate [Advair Diskus]) were approved for children in the age group 4 to 11 years old, but on the basis of data that were less than adequate for the youngest children in this group.

At least one requested study of asthma in a younger age group (birth up to 4 years of age for albuterol sulfate [Ventolin HFA]) reported the use of alternative endpoints. These involved asthma symptom scales that used parents' assessments of symptoms (cough, wheeze, and shortness of breath) in one trial and a clinician assessment using the Modified Tal Asthma Symptoms score, which "included components of respiratory rate, wheezing, cyanosis, and accessory respiratory muscle utilization" (Wang, 2008, p. 14). (In an Internet search, the committee did not find an assessment of the latter instrument.)

For the assessment of studies of pantoprazole sodium (Protonix) for the treatment of gastroesophageal reflux disease (GERD), the clinical review explicitly noted that different symptoms in different age groups required different efficacy endpoints (Chen, 2009). The reviewer also noted concerns, expressed by a consultant from the agency's study endpoints and labeling development team, about the appropriate description for

labeling purposes of measures for infants (vomiting/regurgitation, irritability/fussiness, refusal to feed, choking/gagging, arching back) that were observer (parent) rather than patient based. The consultant also observed that the sponsor did not discuss translation or cultural adaptation of the measures for infants, even though the trial had sites in six countries other than the United States.

On occasion, FDA and a sponsor may not identify a measure suitable for a specific age group, and FDA may waive studies required under PREA for that group. For example, when FDA approved dextromethorphan hydrobromide and quinidine sulfate (Nuedexta) for the treatment of pseudobulbar affect, it waived required studies with children less than 2 years of age. The approval letter explained that the condition "involves exaggerated or contradictory episodes of laughing or crying given the patient's actual emotional state" and "verbal and non-verbal communication is not adequately developed [in this age group] to allow for accurate appraisal of the patient's actual emotional state" (Katz, 2010, p. 3).

Use of Extrapolation

Chapter 1 described the FDA initiative in the early 1990s to increase pediatric studies. Among other steps, FDA allowed, under certain circumstances, the extrapolation of efficacy findings from studies with adults to children. Specifically,

> a pediatric use statement may also be based on adequate and well controlled studies in adults, provided that the agency concludes that the course of the disease and the drug's effects are sufficiently similar in the pediatric and adult populations to permit extrapolation from the adult efficacy data to pediatric patients. Where needed, pharmacokinetic data to allow determination of an appropriate pediatric dosage, and additional pediatric safety information must also be submitted. (59 FR 64240 at 64241)

In 2007, FDAAA added that "a study may not be needed in each pediatric age group if data from one age group can be extrapolated to another age group" (21 USC 355C(a)(2)(B)(ii)).[8]

Allowance for the use of extrapolation is intended to make pediatric drug studies less onerous and thereby increase the number of such studies undertaken. Although the allowance in 1994 for extrapolation of efficacy to pediatric age groups had little effect on its own as a stimulus to pediatric studies, it became more significant after Congress created the incentives and requirements for pediatric studies under BPCA and PREA and their predecessor policies.

[8] In addition to the FDA provisions for extrapolation that were explicitly directed at pediatric studies, FDA also has more general authority to determine effectiveness based on "data from one adequate and well-controlled clinical investigation and confirmatory evidence (obtained prior to or after such investigation)" (21 USC 355(d)). That is, legislation provides for one form of what FDA terms partial extrapolation to be used by sponsors to support the labeling of products for adult uses.

Decision Tree for Extrapolation Decisions

Working from the regulatory framework described above, FDA has developed a decision tree to guide determinations about when extrapolation can be permitted (Figure 5-1). The determinations can differ by age groups (e.g., with extrapolation accepted for adolescents but not for younger children).

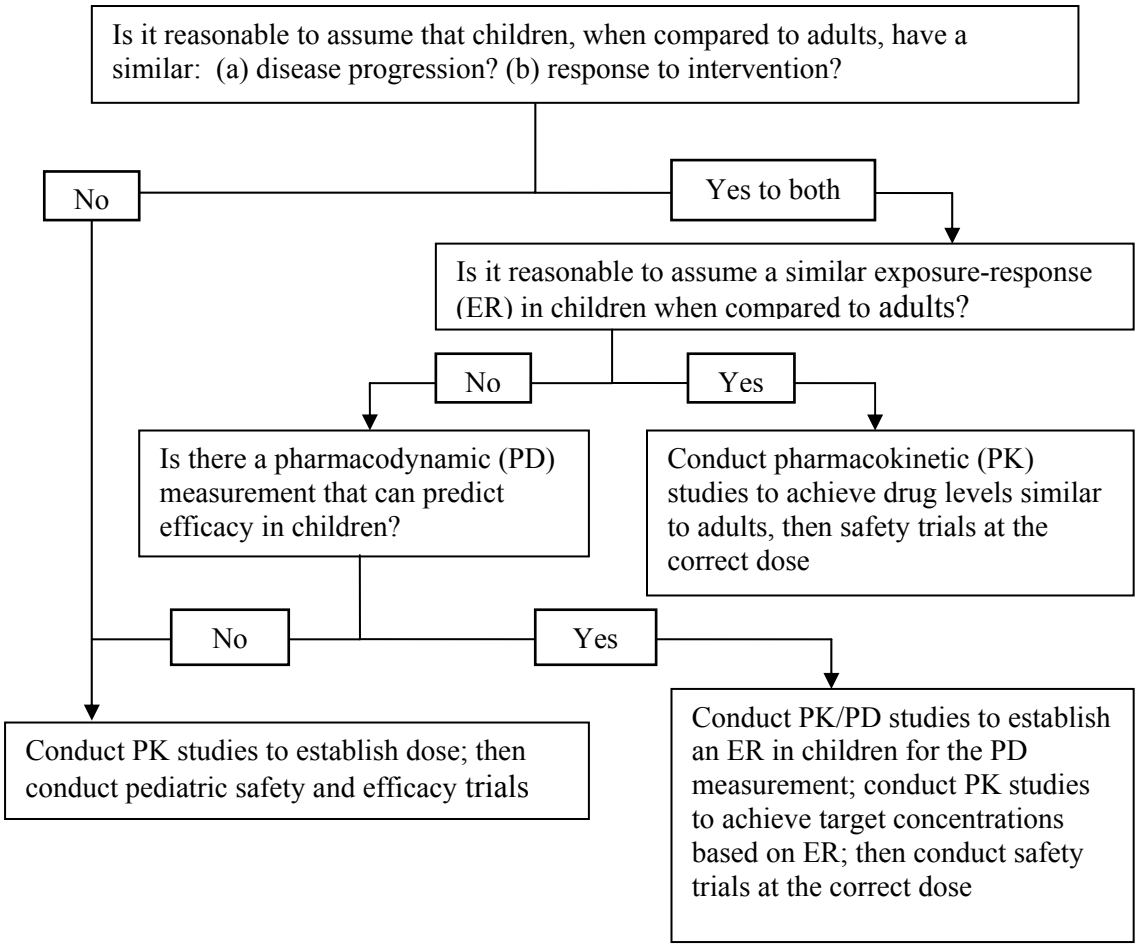

FIGURE 5-1 Use of extrapolation to support pediatric efficacy claims.
SOURCE: Dunn, 2010.

As interpreted by FDA, the extrapolation decision is not a simple "allow" or "do not allow" decision. FDA must also specify the extent to which extrapolation can be relied upon for determinations about efficacy. In guidance issued in 1998, FDA stated that evidence relevant to the determinations about similarity of disease course and diseases effect included "evidence of common pathophysiology and natural history of the

disease in the adult and pediatric populations, evidence of common drug metabolism and similar concentration-response relationships in each population, and experience with the drug, or other drugs in its therapeutic class, in the disease or condition or related diseases or conditions" (CDER/CBER, 1998, p. 8).

Occasionally, the written requests or FDA clinical reviews that the committee assessed used the language presented in the decision tree to acknowledge the use of extrapolation. Only rarely did a written request or FDA clinical review provide a more substantive explanation with references to the scientific literature to justify decisions to allow extrapolation. One example of a justification with explicit citation to the literature appears in the written request for a study of aripiprazole (Abilify) for the treatment of schizophrenia in adolescents:

> Under FDAMA, 1997, adequate assessment of adolescents (data sufficient to support a labeling claim) might be based on a single study in pediatric patients, together with confirmatory evidence from another source, perhaps adult data for that disorder. . . . This approach too requires that the adult data be considered reasonably relevant to the course of the disease and the effects of the drug in the pediatric populations. Although we are aware of only two published placebo controlled studies supporting the efficacy of neuroleptics (haloperidol & loxitane) in the treatment of pediatric schizophrenia . . . we believe that a sufficiently strong case has been made for continuity between adult and adolescent schizophrenia to permit a pediatric claim for a drug already approved in adults to be supported by a single, independent, adequate and well-controlled clinical trial in adolescent schizophrenia. In addition, a pediatric schizophrenia program would need to include pharmacokinetic information and safety information. . . . Finally, although we are requiring only certain specific studies, you will be expected to maximize the potential of the studies to demonstrate an effect of the drug in adolescents, if there is one. Toward this end, then, we urge you to perform additional studies (see below) in order to ensure that the required studies meet this goal. (Temple, 2003, pp. 6–7)

FDA requests and reviews have become somewhat more consistent in providing justification for extrapolation. Such justifications are often limited in their descriptions and citations of relevant literature. FDAAA specifies only that "a brief documentation of the scientific data" supporting a conclusion about the use of extrapolation be included in agency reviews (21 USC 355c(a)(2)(B)(iii)). Nonetheless, given the significance of the reliance on extrapolation, it would be desirable for requests and reviews to provide the public with a justification somewhat fuller than that now provided in each case in which the agency accepts full or partial extrapolation.

Recently, an FDA working group on extrapolation has developed a categorization scheme to label and describe the basic options (Dunne, 2011b, unpaged). They include:

- No extrapolation of efficacy: FDA requires pharmacokinetic data and demonstration of safety and efficacy from two adequate, well-controlled pediatric trials (or from a sequential response and safety trial strategy for oncology products).
- Partial extrapolation of efficacy from studies with adults (or other pediatric age group) with a controlled efficacy trial: FDA requires pharmacokinetic data and confirmation of efficacy and assessment of safety from one adequate and well-controlled pediatric trial.
- Partial extrapolation of efficacy from studies with adults (or other pediatric age group) without a controlled efficacy trial: FDA specifies other acceptable sources of pharmacokinetic, safety, and efficacy or response data.
- Complete extrapolation of efficacy from studies with adults with assessment of safety: FDA requires only safety data or requires safety and pharmacokinetic data to assess age-appropriate dosing.

Extent of Use of Extrapolation

The FDA working group on extrapolation has analyzed the use of extrapolation studies requested under BPCA based on NDA submissions received between February 1998 and February 2009 (Dunne et al., 2011b). As shown in Table 5-2, a 2010 poster presentation reported that 29 (17 percent) of 166 submissions of requested studies involved no extrapolation of efficacy, 24 (14 percent) involved the complete extrapolation of efficacy. The modal submission (67 [40 percent]) included one controlled safety and efficacy trial with additional pharmacokinetic data (which could be obtained during the safety and efficacy trial). For the most part, the fewer the data on efficacy requested by FDA, the more likely it was that a later application for a new or expanded pediatric indication would be approved (Table 5-2). The analysis did not examine the use of extrapolation in studies required under PREA.

TABLE 5-2 FDA Analysis of Use of Extrapolation of Efficacy from Adult to Pediatric Population, Studies Conducted Under BPCA, 1998 to 2009

	No. of Studies with Characteristic/Total No. of Studies (%)	
Extrapolation of Efficacy from Adults or Other Sources	Use for Products with Written Request	New/Expanded Pediatric Indication Achieved
No extrapolation (two WCT[a])	29/166 (17)	10/29 (34)
Partial extrapolation (one WCT)	67/166 (40)	35/67 (52)
Partial extrapolation (other)	46/166 (27)	34/46 (74)
Complete extrapolation	24/166 (14)	15/24 (62)

[a] WCT indicates data required from an adequate well-controlled safety and efficacy clinical trial or, for oncology products, from a two-stage trial process to assess response and safety;
SOURCE: Dunne et al. (2011b).

For its sample, the committee examined FDA's acceptance of extrapolation to support labeling changes resulting both from studies requested

under BPCA and studies required under PREA. Because the use of extrapolation was often not mentioned explicitly, the committee had to infer FDA's reliance on it. For this analysis, as for the one described above, the more extensive that FDA's acceptance of extrapolation was, the more likely the agency was to approve labeling for a pediatric age group (Table 5-3).

TABLE 5-3 Use of Extrapolation for IOM Sample of BPCA and PREA Labeling Changes

	No. (%) of Studies	
Use of Extrapolation	Extent of Use	Indication Granted, by Extent of Use
Extrapolation not accepted (two WCT)	17/55 (31)	8/17 (47)
Partial extrapolation accepted (one WCT)	26/55 (48)	15/26 (58)
Partial extrapolation accepted (other data)	6/55 (11)	5/6 (83)
Complete extrapolation accepted	1/55 (2)	1/1 (100)
Other	5/55 (9)	1/5 (20)

NOTE: Data are for 55 actions, including different decisions for different age groups. WCT indicates data required from an adequate well-controlled safety and efficacy clinical trial or, for oncology products, from a two-stage trial process to assess response and safety; other indicates that the study could involve various combinations of sources of pharamcokinetics, safety and efficacy, response, or activity data. The category "other" includes some submissions for which efficacy were not requested; one for which FDA stated that two WCTs were required but the sponsor only submitted one (which did not show efficacy); and one that included no new pediatric studies.

For written requests, FDA may reject a sponsor's proposal for the use of partial extrapolation from adult studies. For example, in the case of the drug buspirone hydrochloride (Buspar), FDA wrote the sponsor, "While we acknowledge your . . . commitment to conduct two clinical trials for this indication, we do not believe that your new proposal to submit one completed clinical study and one completed pediatric pharmacokinetic study, as a substitute for submitting two completed clinical studies, would be sufficient to support the safety and effectiveness [of the drug] . . . in the pediatric population and to qualify for pediatric exclusivity" (Temple, 1999, p. 1).

As noted earlier, FDA may allow the use of extrapolation for one age group but not another. In a request for studies of pantoprazole (Protonix) for treatment of erosive esophagitis and nonerosive GERD, FDA concluded that efficacy could be extrapolated from adult data to children 1 to 17 years of age because pathophysiology was similar in the two groups. However, for children younger than age 1 year, the agency concluded that extrapolation was not acceptable because, as described in the clinical review, "the pathophysiology of GERD in infants is believed to be unique" and "symptomatology and prognosis differ between infants and individuals greater than age 1 year" (Griebel, 2009). Nonetheless, the agency did not request two well-controlled safety and efficacy studies for infants. Rather, it requested one such study and another pharmacokinetic, pharmacodynamic, and safety study (Raczkowski, 2001). According to FDA's current scheme for categorizing determinations, the request allowed for the use of partial extrapolation on the basis of one safety and efficacy trial in the age group 1 month up to 1

year old. As it turned out, the studies did not support efficacy in children in this age group (see Chapter 6).

CONCLUSIONS

In general, FDA reviewers were careful and thorough in identifying drug-related adverse events, assessing their significance, and reaching conclusions about the safety profile of drugs evaluated in studies with children and the need for any changes in the safety elements of a product's labeling (if it was already labeled). Summary assessments of a product's safety profile were generally accompanied by an identification of serious adverse events.

The committee noted variations in the thoroughness of reviews, although recent reviews are generally more thorough and complete. To further improve the quality of reviews, the committee believes that *it is time for CBER to adopt formally a systematic, standardized template for clinical and other reviews similar to that used by CDER.* The committee also encourages FDA divisions to continue to guide reviewers to follow the safety assessment template, to provide explicit statements about their risk-benefit assessments, and to state clearly their overall conclusions about a product's safety profile and significant or common adverse events.

If successfully implemented, the agency's new guidance on safety reporting for clinical trials should improve identification and assessment of treatment-related adverse events and thereby provide a better foundation for conclusions about a drug's safety profile with pediatric use. Likewise, the structured benefit-risk assessment framework promised by the agency could make an important contribution to FDA's assessments of pediatric drug studies.

Pediatric studies of drug safety and effectiveness over the long term are important but not commonly requested or required. The 1-year safety reviews mandated by Congress appear to provide a useful opportunity for FDA to examine safety experience and to consider overall safety information after products have had labeling changes based on pediatric studies. In several instances, the reviews have led to revisions of safety information in product labeling or pending recommendations for such changes.

Still, the lack of information about the long-term safety of drugs is a particular worry for developing children—both for drugs that may be used for decades for chronic conditions and for drugs for which short-term use may have adverse consequences months or years later. Given such concerns, *FDA might more frequently use its expanded authority to require sponsors to undertake postmarket, follow-up studies of drug safety in pediatric populations.*

Although agency staff generally state that the agency does not accept the extrapolation of safety from studies with adult or other pediatric populations, the committee found examples of such extrapolation. This may be appropriate in unusual circumstances, but a public explanation and justification of these circumstances is desirable.

For the most part, FDA's specification of efficacy endpoints appears to be reasonable, including the use of alternative endpoints when measures used for adults are not appropriate. Written requests and clinical reviews rarely discuss the rationale for

endpoints, whether they are alternative or not. *For alternative endpoints in particular, FDA should consider providing an explicit discussion of their use, including whether they have been validated in studies with children in the age groups to be studied.*

FDA and sponsors rely extensively on extrapolation of efficacy, usually based on requirements for the submission of some efficacy, response, or activity information as well as pharmacokinetic and safety data. The committee found that the justifications were often limited in their descriptions and citations of relevant literature, and Congress requires only brief documentation for the use of extrapolation. Nonetheless, *it would be desirable for requests and reviews to provide the public with a justification somewhat fuller than that now provided in each case in which the agency accepts full or partial extrapolation.*

The committee recognizes that providing the additional justifications and explanations suggested here adds to the demands on agency staff. In some cases, internal documents (e.g., memoranda for PeRC meetings) or sponsor submissions may already provide much of the basis for such explanations. Overall, the committee believes that the significance of the judgments for which more explicit public rationales or justifications are suggested warrants the additional attention.

6
BPCA, PREA, and Drug Studies with Neonates

Chapter 2 discussed how children differ from adults in their response to medications and how neonates, in particular, differ not only from adults but also from older infants and children. As an example of unexpected responses in neonates, it cited the belated discovery in the 1950s of the toxic effects of chloramphenicol when it was used to treat infections in neonates. At roughly the same time, doctors learned that another treatment (penicillin and sulfisoxazole) that had come into use without controlled testing was associated with an increased risk of death attributed to kernicterus (brain injury from elevated bilirubin) (Robertson, 2003a, 2003b). Not long after that, yet another anti-infective (novobiocin) was discovered to pose similar risks to neonates, but this discovery, based on clinical surveillance, came while the product's use was still limited. As described later in this chapter, anti-infectives lead the list of drugs with labeling changes made on the basis of neonatal studies requested under the Best Pharmaceuticals for Children Act (BPCA) and required under the Pediatric Research Equity Act (PREA).

Despite substantial advances in the understanding of neonatal pharmacology, improved resources for neonatal clinical studies, and explicit inclusion of neonates as a relevant age group for studies conducted under BPCA, the limited testing of medications in this vulnerable age group is a continuing concern. One of the tasks for the Institute of Medicine (IOM) committee was to examine the use of neonatal assessment tools in studies conducted under BPCA and PREA or predecessor policies. This chapter reviews data on the extensive off-label use of medications for treatment of neonates and highlights the challenges of conducting studies with this age group. It then discusses neonatal assessments resulting from requests under BPCA or requirements under PREA.

MEDICATION TESTING AND MEDICATION USE WITH NEONATES

Challenges of Medication Testing with Neonates

Testing the safety and efficacy of medicines in neonates is particularly challenging (see, e.g., Kearns et al., 2003; NICHD/FDA, 2004; Anand et al., 2005; Baer, 2009; Rakhmanina and van den Anker, 2009; PhRMA, 2011a). The short neonatal period (28 days) presents a brief window for study enrollment and participation. Ethical issues may also complicate enrollment. Especially for parents of a premature or sick newborn, the

period after birth is a stressful time. In some cases, very ill newborns may be quickly transferred to hospitals with critical care capacities, resulting in the separation of the newborns from their parents and complications for researchers seeking fully informed parental permission for a child's participation in research (see, e.g., Nicklin and Spencer, 2004, and Chapter 4). Although some studies with neonates have involved hundreds of neonates, small sample sizes are common, thus limiting the likelihood that less frequent adverse effects of medications or medication interactions will be detected in clinical trials.

Moreover, variability within the neonatal population is considerable and can influence the pharmacokinetics, pharmacodynamics, safety, and efficacy of medications. For example, neonates of the same chronological age—as dated from birth—may differ substantially in weight (e.g., from weights of about a barely viable one-half kilogram to more than 6 kilograms) and in developmental maturation (e.g., their ability to metabolize and respond to drugs). This variability, which is often a function of gestational age (dated from the first day of the mother's last menstrual period), can significantly alter how drugs affect and are affected by the body.

Chapter 2 emphasized the need to consider gestational as well as chronological age in designing pharmacokinetic and other studies and to be careful about extrapolating from older pediatric populations. For example, in the early 1980s, vitamin E was administered parenterally to premature infants to supplement antioxidant defenses and reduce the risk of thrombocytosis, hemolytic anemia, and edema. This practice, initiated without systematic prospective evaluation in studies, resulted in 38 deaths (Brion et al., 2003). It remains unclear whether adverse effects resulted from the vitamin E itself, from other components of the product (e.g., polysorbates), or from an unidentified contaminant.

Gestational as well as chronological age and other variability among neonates may also affect the feasibility of certain research procedures. For example, repeated or relatively large blood draws for research purposes may be safe for larger but not smaller neonates, who could be put at risk of anemia (Proytcheva, 2009).

As with any age group, investigators must consider how different disease processes (e.g., systemic infection or cardiac anomalies) may affect the pharmacokinetics, pharmacodynamics, safety, and efficacy of medications used with neonates. Likewise, they must consider how variability in severity, etiology, or other characteristics for the same condition may affect study results. In addition, the exposure of ill neonates to many different medications and therapeutic agents has the potential to create drug-drug and drug-disease interactions that confound study findings.

Even more than is the case with other age groups, short- and long-term risks to neonates may not be identified through preclinical testing and relatively small, short-term clinical investigations that typically support drug approval for this age group. Possible adverse effects of trial medications on neurological and other aspects of development may not be detectable for months or years. Some have cited this possibility to be a concern in Food and Drug Administration (FDA) assessments of the effects of anesthetics on neonates (Rappaport, 2011d). Questions about the long-term effects of morphine use to relieve pain in neonates (de Graaf et al., 2011) and dexamethasone, a corticosteroid used to prevent chronic lung disease in preterm newborns, have likewise been raised (see, e.g., Yeh et al., 2004; Lee et al., 2008; and Doyle et al., 2010).

Concerns about long-term effects of medication use go beyond neurological outcomes. For example, studies are assessing whether certain treatments for premature

newborns play a role in the association between prematurity and the development in early childhood of hepatoblastoma, the most common type of liver cancer in children (see, e.g., MCC, 2010 and Nishi, 2010).

Postmarket reporting and analysis of adverse events can identify some short- and long-term risks that drug trials do not. For example, prompted by postmarket reports of fatalities among neonates, FDA issued alerts and directed revisions in the labeling of the antibacterial agent ceftriaxone (Rocephin and generic versions) to warn that the drug should not be used with neonates who are receiving intravenous medications that contain calcium (see Genentech, 2010a).

To cite another example, in 2011, after postmarket reports of life-threatening cardiac and other events in premature babies treated with lopinavir-ritonavir (Kaletra) oral solution, FDA revised the product's labeling to add a warning against use with infants under 14 days of age (Klein and Struble, 2011). According to the FDA, the risk may be related to the lopinavir, propylene glycol, or ethanol in the drug. The last two substances compete with lopinavir and ritonavir for the same metabolic enzymes, which are known to be immature at birth. The drug had been labeled for use only by infants ages 14 days or over in 2008, but off-label use to treat younger neonates was common (Boxwell, 2011). In addition to underscoring the importance of postmarket safety surveillance, this example also highlights the importance of testing not only medications but also ingredients in the medications that are regarded as inactive (Committee on Drugs, 1997).

Medications Commonly Used with Hospitalized Neonates

As documented later in this chapter, studies with neonates have contributed to relatively few labeling changes that have resulted from studies conducted under BPCA and PREA. Many more drugs are used off-label in this age group. Most studies of such use focus on drugs used in neonatal intensive care units. They suggest that many if not most medications used in such units have not been studied with this population or at least not studied to the standard required to label the drug for use with neonates. For example, a study of medication use in neonatal care units in the United Kingdom examined whether the medicines used were licensed for use by term or preterm infants and had dosing information in the *British National Formulary for Children* for both categories of neonates (Turner et al., 2009). The researchers found that licensing and dosing information was complete for only a quarter of the uses (3,924 uses of 119 different medications) and that 4 percent of uses involved medications that had no licensing or dosing information for term or preterm infants. The therapeutic area most often identified with incomplete information was chronic lung disease. An earlier study performed in the United Kingdom reported that up to 93 percent of neonates in intensive care units received at least one treatment of a medication off-label (Conroy and McIntyre, 2005). Studies conducted elsewhere show a generally similar picture (Jong et al., 2001 [Netherlands]; Barr et al., 2002 [Israel]; O'Donnell et al., 2002 [Australia]; Cuzzolin et al., 2006 [review]; Neubert et al., 2010 [Germany]; Yang et al., 2010 [United States]).

Given the large number of neonates who receive intensive care, the potential for harm from the use of medications not studied or incompletely evaluated in studies with neonates needing intensive care is a significant concern. Of the more than 4 million babies

born annually in the United States, an estimated 6 percent are admitted to neonatal intensive care units (Osterman et al., 2009).

Using data from a large U.S. data set, Table 6-1 shows therapeutics commonly used with neonates admitted to intensive care. Of the 10 most commonly used medications, 6 have some information on dosing in the labeling and 4 do not.

TABLE 6-1 Therapeutics Commonly Used in the Neonatal Intensive Care Unit

Medication	% Exposed	FDA Labeling for Use with Neonates
Ampicillin	74	None
Gentamicin	68	Labeled for use (premature and term)
Cefotaxime	36	Labeled for use
Caffeine [citrate]	19	Labeled for use for ages 28 up to 33 weeks
Furosemide	19	Safety warnings (premature and term neonates)
Vancomycin	17	Dosing (premature and term neonates)
Beractant	14	Labeled for use for premature newborns
Metoclopramide	11	Cautions
Aminophylline	11	Labeled for use (term neonates)
Dopamine	10	None (mention of reports)

NOTES: If the information on dosing for neonates appears in the dosing and administration section of labeling, the product is categorized as labeled for use in the age group. Dosing-relevant information may also appear in the pharmacology section or elsewhere in the label. These products tend to have labeling that is less clear and explicit than labeling for more recently approved products

SOURCES: The information in the left and center columns is from Berezny et al., 2011, based on neonatal intensive care unit data from Clarke et al., 2006. Labeling information is based on the results of searches at Daily Med (a website with drug labeling information, including for generic medications, sponsored by the National Institutes of Health).

One of the medications in the table, caffeine citrate, was the subject of a recent report by investigators who described the results at the 5-year point of a long-term randomized, placebo-controlled study to determine whether the use of drug to treat apnea of premature "has lasting benefits or newly apparent risks at early school age" (Schmidt et al., 2012, p. 275). They reported that the early benefits of the therapy diminished as children developed but also that the absence of adverse effects was reassuring. Further follow-up of the children at ages 11 to 12 years will focus on differences in motor and visual impairment as predictors of academic success. The study, which was funded by the Canadian Institute for Health Research, illustrates the importance of long-term studies of the benefits and risks of neonatal therapies and the importance of public funding for such studies, particularly for long-marketed drugs.

Other (not yet published) data on medications used to treat neonates in children's hospitals show some differences in the rankings of commonly used drugs compared to Table 6-1 (data supplied by Chris Feudtner, Center for Pediatric Clinical Effectiveness, Children's Hospital of Philadelphia, January 23, 2012; for information about the data set and information about drugs commonly used with older children, see Feudtner et al., 2012). Excluding products such as intravenous fluids, vitamins, hyperalimentation products, heparin flush products, and dextrose water, the most commonly used products

included ampicillin, gentamicin, heparin, potassium chloride, acetaminophen, fentanyl, cefotaxime, erythromycin, lidocaine, and morphine. In this listing, the prominence of medications for pain is notable.

A recent FDA workshop on clinical trials for pediatric analgesia noted the lack of clear evidence for the efficacy for acetaminophen or nonsteroidal anti-inflammatory drugs in neonates (Berde et al., 2012). No fentanyl product is labeled for neonatal use. Labeling for lidocaine hydrochloride injection products is generally vague (recommending merely reduced dosing commensurate with age, weight, and physical condition). As described later in this chapter, the National Institutes of Health (NIH) is supporting a study of morphine in the treatment of neonates.

DRUGS STUDIES WITH NEONATES CONDUCTED UNDER BPCA AND PREA

One question for the IOM committee was how to define *neonatal assessment tools*, a term specified but not defined in the statement of task. Were they simply any endpoints used in studies with neonates, or were they composite endpoints involving more than one such measure? Or was something more comprehensive intended?

A presentation by FDA at the committee's first meeting in December 2010 suggested that the term might be defined more broadly than simply alternative endpoints or outcome measures used with neonates (Nelson, 2010). The committee decided to take a broader approach and examined neonatal assessments or studies that were conducted in response to requests under BPCA or requirements under PREA. The committee also considered in more detail three clinical areas that have been the focus of numerous written requests for drug studies that included neonates: HIV infection, bacterial conjunctivitis, and gastroesophageal reflux disease (GERD).

Numbers and Origins of Studies with Neonates

To assist the IOM, FDA supplied a table of information about products with labeling changes related to neonatal studies that were conducted under BPCA and PREA from July 1, 1998, through December 31, 2010. The addendum to this chapter summarizes this information. FDA created the table from a master list of labeling changes. As explained in Appendix A, that list excluded biologics that are regulated under the Public Health Service Act and that had labeling changes before September 27, 2007. For the period after September 2007, FDA lists no biologics as having labeling changes made on the basis of studies with neonates.[1] The master list also excludes labeling changes attributable to other policies, for example, the Orphan Drug Act. An example of an orphan

[1] One product in the FDA list, hydroxyethyl starch (Voluven; a plasma volume expander), is under the regulatory oversight of the Center for Biologics Evaluation and Research, but it was approved in 2007 through a New Drug Application under the Food, Drug, and Cosmetic Act and does not meet the definition of a biologic. Appendix Table D-2, which shows biologics for which pediatric studies have been registered at ClinicalTrials.gov, lists some trials of biologics that are described as including neonates, e.g., bevacizumab (Avastin) for retinopathy of prematurity. These studies may result in future labeling changes.

drug evaluated in studies with neonates is antihemophilic factor (recombinant) ReFacto, a biologic.

Of the approximately 365 labeling changes that FDA identified for the period from 1998 to 2010 that involved the submission of new pediatric studies, only 23 (6 percent) involved the addition of information from studies that included neonates.[2] One other product (moxifloxacin [Vigamox]) that was studied with neonates and also older children had a labeling change that did not mention specific results from the studies of neonates. The list provided by FDA also includes four additional products for which labeling changes were not made but for which FDA had granted exclusivity for studies conducted in response to written requests. Three of these requests were for studies of bacterial conjunctivitis in neonates only and involved products that were previously approved for treatment of the condition in children 1 year of age or older.

Of the products included in the addendum table (including those for which no labeling change occurred), the requested or required studies of neonates are concentrated in a few therapeutic areas:

- Infectious conditions (14 products studied, including 7 for treatment of HIV infection and 4 for treatment of bacterial conjunctivitis)
- Gastroenterology (4 products studied, all for treatment of GERD)
- Cardiology (3 products studied)
- Anesthesia (3 products studied)

For the total of 28 products studied with neonates and listed in the addendum to this chapter, the agency attributed studies for 16 to BPCA alone, 3 to PREA alone, and 9 to BPCA and PREA. For the five products for which neonatal studies had been conducted but no labeling changes based on neonatal studies had been made, all are attributed to BPCA. For the recent period after the reauthorization of BPCA and PREA in September 2007, the Government Accountability Office (GAO) reported that at least 130 products had labeling changes that were linked to the two policies (GAO, 2011) and that 9 (7 percent) of these products were investigated in studies with neonates. For these nine products, seven labeling changes were related to BPCA and two were related to PREA.

Overall, BPCA accounts for a larger share of labeling changes involving studies with neonates (48 percent) than is the case for labeling changes across all pediatric age groups (35 percent), and PREA accounts for a much lower percentage (13 percent for the neonatal age group versus 54 percent for all pediatric age groups). For studies attributed by FDA to both BPCA and PREA, the figures are 39 versus 11 percent, respectively.

[2] Additional studies with neonates may be under way as a result of written requests under BPCA, but FDA does not make such information public. In FDA's database for tracking postmarket study requirements and commitments, the committee identified examples of required studies that have been deferred for the neonatal age group. (The database can be accessed at http://www.accessdata.fda.gov/scripts/cder/pmc/index.cfm. Some of the 339 entries do not note the age groups for deferred studies.) For example, the database lists as "ongoing" a study of difluprednate ophthalmic emulsion (Durezol) 0.05% to treat postoperative inflammation in children 0 to 3 years of age who undergo cataract surgery. To cite another example, a study of the use of tenofovir disoproxil fumarate (Viread) in combination with other antiretroviral agents to treat HIV infection in children from birth to 2 years of age is described as "delayed" pending the completion of safety assessments from studies with children 2 to 18 years of age.

Chapter 7 reports that FDA characterized approximately 66 percent of studies for all the BPCA- and PREA-related labeling changes approved since September 2007 as efficacy studies. Of the 23 products with labeling changes related to studies with neonates (since July 1, 1998), 14 (61 percent) of the requested or required studies were characterized by FDA as efficacy studies (9 studies) or studies of drug response (5 studies), which reviewers may cite as an indicator of efficacy. All clinical studies, even those that FDA characterizes as pharmacokinetic and pharmacodynamic studies, yield data that FDA evaluates for safety.

One complication in identifying studies with neonates conducted under BPCA or PREA involves studies that included neonates in a group that also included older children. Study descriptions do not always make clear how many neonates—if any—were actually included in the study group. In compiling the list of products with labeling changes based on studies with neonates, FDA excluded some products for which a specified study age range included neonates but no neonates were actually enrolled according to the FDA reviews. (For an example, see the review of antihemophilic factor, recombinant [Kogenate FS], a biologic product [Jain, 2008]).[3] For other products for which information was not explicit, the inclusion of neonates in studies was inferred from the wording of the reviews or labeling, for example, when the indication for use of a product was extended from a lower age of 12 years to a lower age of 14 days.

Some of the studies with neonates listed in the addendum involved very small numbers. For example, according to the labeling for the 2004 approval of fenoldopam (Corlopam) for in-hospital, short-term reduction in blood pressure, two neonates were among the 77 children from birth to 12 years of age enrolled for study of the relationship between drug concentration and vital signs (Hospira, 2006). For the study of sotalol hydrochloride (Betapace) for treatment of arrhythmias, a single-dose pharmacokinetic study included two neonates and a multiple-dose pharmacokinetic and pharmacodynamics study included seven (Karkowsky, 2000). In contrast, more than 2,100 preterm neonates were enrolled in the safety and efficacy studies of inhaled nitric oxide (INOmax) for prevention of chronic lung disease (bronchopulmonary dysplasia) (Witzmann, 2010). (Both drugs were studied in response to written requests.)

Of the 23 changes in labeling noted in the table in the addendum, almost half (n = 11) occurred between January 1, 2007, and December 31, 2010.[4] For safety and efficacy studies in particular, it frequently takes many years from the time of a request or requirement for a study to be initiated, completed, and analyzed before the results are submitted to and assessed by FDA. For example, for one of the products (clopidogrel [Plavix]) for which neonatal and infant studies were requested and for which a labeling change was approved in May 2011, FDA issued the original written request in 2001 and amended it in 2007 (Behrman, 2001b and Rose, 2010). In some cases, the time span from request to labeling is much shorter because the requested studies were completed prior to the request. For example, FDA issued a written request in April 2010 for a study of nitric oxide (INOmax) and granted exclusivity in November of the same year, with a labeling

[3] FDA also excluded studies for two products in which only one neonate was identified in the relevant study group (albuterol sulfate HFA inhalation aerosol [Ventolin HFA] and omeprazole magnesium [Prilosec]) (personal communication, Catherine Lee, Office of Pediatric Therapeutics, FDA, June 17, 2011).

[4] In 2011, FDA approved labeling changes for more products for which sponsors submitted information from studies with neonates. These products included clopidogrel (Plavix) and esomeprazole intravenous (Nexium).

change following in December 2010 (Witzmann, 2010). Two of the studies for which information was submitted were completed in 2005, and a third study was completed in 2008.

Written Requests, PREA Requirements, and Labeling Changes

Written Requests Under BPCA

In the table supplied by FDA and presented in the addendum to this chapter, studies of 25 of 28 products were associated with written requests under BPCA. As noted above, this group included five products for which no information from the neonatal studies was added to the product label. Some of the requests specified only a study with neonates (e.g., inhaled nitric oxide [INOmax] for bronchopulmonary dysplasia), whereas others sought studies for children in more than one age group. Although FDA letters (particularly recent letters) describe the reasons for waivers of studies required under PREA, written requests typically do not explain the basis for excluding an age group.

FDA publishes a list of products (active moieties) for which written requests for study have been issued since 1998, but the list does not identify the age groups or indications included in the request, nor does it identify the requests that have been declined by sponsors. As a result, the committee could not determine how many written requests issued since 1998 had specified studies with neonates, how many such requests had been declined by sponsors, how many initially requested studies with neonates had been eliminated through amendments to requests, or how many requested studies with this age group might be under way or might have been submitted to FDA with no announcement so far of the results of the FDA evaluation.

For the period after the reauthorization of BCPA in 2007, the GAO reported that 3 of the 37 written requests issued by FDA mentioned a study with neonates as an option but not a requirement (GAO, 2011). A fourth request specifically required a study with neonates to meet the terms of the request. The GAO report did not discuss whether the sponsor had accepted or declined the request. In the requests and requirements for studies examined by the committee, the age groups omitted typically were not limited to neonates but covered a broader age range, for example, children less than 6 years of age.

One instance of a neonatal study originally requested but then removed involves darunavir (Prezista) for the treatment of HIV, which was the subject of both a BPCA request and a requirement under the Pediatric Rule. The original request issued in 2006 included neonates (Murray, 2006), but the amended request issued in 2007 changed the age range—without comment—to children 3 years of age to adolescence (Murray, 2007). In 2008, a letter approving an expanded indication and new dosing regimen for the product waived required studies for the same age group (Murray, 2008). This letter cited "evidence [from studies with juvenile rats] strongly suggesting that the drug product would be unsafe in this pediatric group" (Murray, 2008, p. 1).

In explaining the small number of requests for studies with neonates, FDA officials told GAO that the "neonate population has diseases that are very different from other pediatric populations" (GAO, 2011, p. 41). Another constraint is that many of the drugs

frequently used to treat neonates were approved many years ago and have no remaining patent life or exclusivity. Thus, the primary incentive under BPCA has no relevance. As discussed below, a number of off-patent drugs have been identified as priorities for study under the BPCA program at NIH.

Pediatric Rule and PREA Requirements

As described in Chapter 3, PREA (and the earlier Pediatric Rule) applies to original or supplemental New Drug Applications (NDAs) and Biologics Licensing Applications (BLAs) for approval of a new active ingredient, a new indication, a new dosage form, a new dosing regimen, or a new route of administration, unless FDA has waived or deferred the requirement. The agency can require pediatric studies only for the indication that is the subject of an NDA or BLA submission. Of the 28 products listed in the table in the addendum to this chapter, 12 had studies that were associated with requirements under PREA, although just 3 of these involved a PREA requirement only.

The committee found no comprehensive information on the extent to which required pediatric studies have been waived, deferred, or fulfilled for neonates. Of the overall sample of 45 labeling changes that the committee assessed, 5 were for products for which FDA had initially deferred studies for age groups that included neonates. Subsequently, FDA released two of the sponsors from the requirements for those studies. One had been for the study of adalimumab (Humira) in the 0- to 4-year-old age group, and the other was for a study of omalizumab (Xolair) in the 0- to 5-year-old age group (Roca, 2008; Gilbert-McClain, 2010).

For the products in the committee's sample, none of the age groups waived from the requirement for study was limited to neonates. In addition to juvenile rheumatoid arthritis, conditions for which FDA has waived studies with neonates (among other young children) include autism, neutropenia associated with myelosuppressive anticancer drugs, osteogenesis imperfecta, asthma, migraine, atopic dermatitis, and tonsillitis.

In the committee's sample and in general, FDA's usual explanation for a waiver (if provided) is that the studies are impractical or impossible because the condition is rare or is not diagnosed in the age group in question (CDER, 2010).[5] Supporting data are rarely if ever cited, and prevalence data for neonates (and other pediatric subgroups) may not, in fact, be available in many cases. In the view of the committee, the conditions cited in the preceding paragraph are rare or are not diagnosed in children less than 1 month of age. In discussions with GAO staff, FDA officials explained that the conditions subject to PREA requirements were often conditions "typically applicable to adults and older pediatric populations that would not apply to neonates" (GAO, 2011, p. 40).

By consulting the FDA tracking database for postmarket study requirements and commitments, the committee found recent examples of deferred studies for neonates. For

[5] The age groups covered by waivers and the rationales for waivers may vary from decision to decision involving the same indication and similar products. An example can be cited for products to treat autism. In a 2006 letter for one product, FDA waived study requirements for children less than 2 years of age on the grounds that the condition is difficult to diagnose and treat in that age group (Laughren, 2006); in a 2009 letter involving another product, it waived studies with children less than 5 years old on grounds of impossibility or impracticality (Laughren, 2009a). During that period, FDA began an analysis of the extent to which reasons for waivers of PREA requirements matched the criteria in legislation (CDER, 2010b).

example, in approving rilpivirine (Edurant) for treatment of HIV infection in treatment-naïve adults, FDA deferred required pediatric studies of safety and antiviral activity in children from birth up to 12 years and from 12 up to 18 years (Cox, 2011). In deferring pharmacokinetic, safety, and efficacy studies of ondansetron (Zuplenz) for treatment of postoperative nausea and vomiting in children 0 to 17 years of age, FDA noted that an age-appropriate formulation must be developed for younger patients (Griebel, 2010).

Explanations for deferred studies may note special issues involving neonates. In one recent approval of the continued marketing of an old, previously unapproved oxycodone product, FDA deferred studies with the pediatric population. The summary review for the action stated that knowledge about "the site of action of oxycodone and. . . the developmental maturity of the mu opioid receptor" would allow extrapolation of efficacy for children more than 2 years of age, but efficacy studies for ages 0 to 2 years were necessary (Hertz, 2010b, pp. 6–7).

At least one recent approval letter—for the drug ceftaroline fosamil (Teflaro) for the treatment of bacterial skin infections and community-acquired pneumonia—reflected the consideration of gestational as well as chronological age. It specified PREA requirements for a pharmacokinetic study with five pediatric-age cohorts within the overall age group from birth up to 12 years (Cox, 2010). One of these cohorts was term neonates (stratified by ages 0 to 14 days and 15 up to 28 days), and another was preterm neonates (with the same stratification).[6]

The committee also found several recent examples of waivers of required studies for the neonatal age group. For a combination hydrocodone and pseudoephedrine product (Rezira) for the treatment of colds and coughs, FDA explained the waiver for neonates on the grounds that hydrocodone poses a risk of fatal respiratory depression in this age group (Chowdhury, 2011). In waiving studies for children less than 6 years of age for a sublingual formulation of fentanyl (Abstral) for breakthrough pain for cancer patients, FDA explained that studies would not be feasible because too few children in this age group could use the product appropriately (Rappaport, 2011a). Although data cited earlier show that the drug is frequently used to treat pain in neonates, no fentanyl products are approved for use with neonates (personal communication, Division of Anesthesia, Analgesia, and Addiction Products, FDA, January 23, 2012). Other recent waivers of studies with neonates involved conditions such as schizophrenia, anal fissures, plaque psoriasis, type 2 diabetes, depression, restless leg syndrome, breakthrough cancer pain, insomnia, eradication of *Helicobacter pylori* infection, hepatitis C, and partial onset seizures.

On the basis of its selective review of recent deferral and waiver decisions, the committee has the impression that the agency is more carefully considering the rationale for requiring studies with neonates than was the case in earlier periods, a development that may reflect the involvement of the Pediatric Review Committee (PeRC) as described in Chapter 3. This consideration may include more careful assessment of claims that studies are impractical or impossible because the condition is rare in neonates.

[6] Requirements also included a cerebrospinal fluid concentration trial with at least 12 infants less than 2 months of age as well as separate randomized trials for two infectious conditions with children less than 17 years of age (with no age subgroups specified).

Labeling Changes Resulting from Studies with Neonates

Overall, most of the requested or required studies with neonates did not lead to labeling of the product as safe and effective for use with neonates. For the majority of products, the labeling changed to include some information (e.g., pharmacokinetic data) from the studies, but for five products, as noted earlier, no substantive information from the studies with neonates was included in the labeling. Four of these studies were for bacterial conjunctivitis. For two of these three products with approvals prior to the reauthorization of BPCA in 2007, neither the written requests nor the FDA clinical reviews are public, although as required in 2002, FDA posted brief summaries (less than two pages) of the reviews. Consistent with requirements in the reauthorization of BPCA in 2007, FDA now must make public certain information for products approved after 2007 with exclusivity and no labeling change (see Chapter 3).

Box 6-1 provides examples of the kinds of labeling changes that provided information about the studies conducted with neonates. Some of the examples of labeling changes also illustrate ambiguous or unusual situations. The first example listed involves a study that the FDA clinical reviewer criticized and believed did not fairly meet the terms of the written request, although FDA subsequently decided to grant exclusivity. The second example involves a product for which FDA accepted extrapolation of efficacy in the treatment of acute pain in children ages 2 years and older but required, under PREA, a "randomized, double-blind, adequately controlled study of efficacy, pharmacokinetics and pharmacodynamics" for children less than 2 years of age (Hertz, 2010a, p. 3). Although the dosing and indications section of the label associated with that approval does not include information on dosing for that age group, the pharmacokinetic section of the label does include such information (Cadence Pharmaceuticals, 2010). The review memoranda show considerable amounts of redacted text; it is possible that this text discusses the 47 neonates studied (out of 355 children overall) and provides the rationale for the labeling (Fang, 2009; Spaulding, 2009).

BOX 6-1
Examples of Labeling Changes with Information Based on BPCA- or PREA-Related Neonatal Studies

Clopidogrel bisulfate (Plavix) (NDA 020839/051) (BPCA)
Excerpt from labeling for a change approved in 2011: "Safety and effectiveness in pediatric populations have not been established. A randomized, placebo-controlled trial (CLARINET) did not demonstrate a clinical benefit of clopidogrel in neonates and infants with cyanotic congenital heart disease palliated with a systemic-to-pulmonary arterial shunt. Possible factors contributing to this outcome were the dose of clopidogrel, the concomitant administration of aspirin and the late initiation of therapy following shunt palliation. It cannot be ruled out that a trial with a different design would demonstrate a clinical benefit in this patient population." (Sanofi-Aventis, 2011, p. 3)

Acetaminophen (Ofirmev injection) (NDA 022450) (PREA)
Excerpts from labeling for a change approved in 2010: "A total of 355 pediatric patients (47 neonates, 64 infants, 171 children, and 73 adolescents) have received OFIRMEV in active-controlled (n = 250) and open-label clinical trials (n = 225). . . . The maximum exposure was 7.7, 6.4, 6.8, and 7.1 days in neonates, infants, children, and adolescents, respectively. . . . The safety

and effectiveness of OFIRMEV for the treatment of acute pain and fever in pediatric patients ages 2 years and older is [*sic*] supported by evidence from adequate and well-controlled studies of OFIRMEV in adults. Additional safety and pharmacokinetic data were collected in 355 patients across the full pediatric age strata, from premature neonates (≥32 weeks post menstrual age) to adolescents. The effectiveness of OFIRMEV for the treatment of acute pain and fever has not been studied in pediatric patients <2 years of age. . . . Dosing simulations from pharmacokinetic data in infants and neonates suggest that dose reductions of 33% in infants 1 month to <2 years of age, and 50% in neonates up to 28 days, with a minimum dosing interval of 6 hours, will produce a pharmacokinetic exposure similar to that observed in children age 2 years and older." (Cadence Pharmaceuticals, 2010, unpaged)

Rocuronium bromide (Zemuron) (NDA 20214/030) (BPCA)
Selected excerpts from labeling for a change approved in 2008: "The recommended initial intubation dose of ZEMURON is 0.6 mg/kg, however, a lower dose of 0.45 mg/kg may be used depending on anesthetic technique and the age of the patient. . . . The time to maximum block for an intubating dose was shortest in infants (28 days up to 3 months) and longest in neonates (birth to less than 28 days). The duration of clinical relaxation following an intubating dose is shortest in children (greater than 2 years up to 11 years) and longest in infants. . . . The infusion of ZEMURON must be individualized for each patient. . . . ZEMURON was also studied in pediatric patients up to 17 years of age, including neonates, under sevoflurane (induction) and isoflurane/nitrous oxide (maintenance) anesthesia. Onset time and clinical duration varied with dose, the age of the patient, and anesthetic technique. The overall analysis of ECG [electrocardiographic] data in pediatric patients indicates that the concomitant use of ZEMURON with general anesthetic agents can prolong the QTc interval. The data also suggest that ZEMURON may increase heart rate. However, it was not possible to conclusively identify an effect of ZEMURON independent of that of anesthesia and other factors." (Teva Pharmaceuticals, 2008, unpaged)

6% hydroxyethyl starch (Voluven) (NDA 70012/000) (PREA)
Excerpt from labeling for a change approved in 2007: "Limited clinical data on the use of Voluven® in children are available. In 41 children including newborns to infants (<2 years), a mean dose of 16 ± 9 mL/kg was administered. The dosage in children should be adapted to the individual patient colloid needs, taking into account the disease state, as well as the hemodynamic and hydration status**.** The safety and efficacy of Voluven® have not been established in the age group of 2 to 12 years. Use of Voluven® in children >12 years is supported by evidence from adequate and well-controlled studies of Voluven® in adults and by data from children <2 years old." (Hospira, 2007, p. 4)

Emtricitabine (Emtriva) (NDA 21896/001) (BPCA)
Excerpts from labeling for a change approved in 2006: "The pharmacokinetics of emtricitabine were studied in 20 neonates born to HIV positive mothers. Each mother received prenatal and intrapartum combination antiretroviral therapy. Neonates received up to 6 weeks of zidovudine prophylactically after birth. The neonates were administered two short courses of emtricitabine oral solution (each 3 mg/kg QD × 4 days) during the first 3 months of life. Emtricitabine exposures in neonates were similar to the exposures achieved in patients >3 months to 17 years. . . . During the two short dosing periods on emtricitabine there were no safety issues identified in the treated neonates. All neonates were HIV-1 negative at the end of the study; the efficacy of emtricitabine in preventing or treating HIV could not be determined." (Gilead Sciences, 2008, p. 11)

For the third product listed in Box 6-1, the 2008 labeling change for rocuronium bromide (Zemuron) came almost 10 years after the sponsor's initial proposal for a written request but shortly after the final amendment to the written request. That amendment reduced the number of neonates to be included in the pharmacodynamic study based on the conclusion that study of an additional two neonates would not affect the judgment that each patient would require individual monitoring for the product to be used safely (Schultheis and Roca, 2008).

Examples of Successful and Unsuccessful Studies

Given the several trials with neonates that failed to provide evidence of efficacy or even information for labeling, the committee attempted to identify factors that might be associated with such failures. It examined the trials of drugs for the prevention or treatment of HIV infection in neonates that led to labeling changes (including several with labeling for neonatal use) and compared their characteristics with those of the trials of drugs to treat bacterial conjunctivitis and GERD. All the studies were requested under BPCA.

Studies with Neonates Leading to Important Labeling Changes: HIV Infection

By December 31, 2010, seven requested studies of products to treat HIV infection in neonates had led to the addition of information to product labeling. Four drugs were labeled for use with neonates (one starting at birth and three starting at about 2 weeks of age) (Table 6-2). For the other three drugs, the labeling changes included pharmacokinetic and other information. As noted earlier, FDA recently warned explicitly against the (off-label) use of lopinavir-ritonavir (Kaletra) with neonates less than 14 days of age. In addition, the committee understands that although didanosine (Videx) is labeled for neonatal use, concerns about toxicity limit its use with that age group.

TABLE 6-2 Labeling Changes for Drugs for Treatment of HIV Infection from Studies That Included Neonates

Agent	Ages Studied	Labeling Information (year)
Nevirapine (Viramune)	≥15 days–3 months	Indicated for ages >15 days (2008)
Lopinavir-ritonavir (Kaletra)	≥14 days–6 months	Indicated for ages ≥14 days (2008)
Emtricitabine (Emtriva)	0–3 months	Safety, PK,[a] dosing, but not efficacy (2006)
Nelfinavir (Viracept)	Birth–13 years	PK from birth to 13 years; no reliable data for dosing for ages <2 years (2004)
Lamivudine	≤1 week	Reduced clearance in 1-week-old neonates;

(Epivir)		insufficient information for dosing; limited safety information (2002)
Didanosine	2 weeks–8 months (2002)	Indicated for ages ≥2 weeks (Videx)
Stavudine (Zerit)	Birth–13 days	Indicated for all ages (2002)

[a] PK = pharmacokinetics.
SOURCES: Product labels and FDA clinical reviews.

At the time that the requests were issued (as early as 1999), pediatric studies of HIV infection had several advantages compared with the studies for bacterial conjunctivitis and GERD. These included reasonably straightforward diagnostic criteria and procedures and validated surrogate endpoints, notably, measures based on the HIV-1 RNA viral load. Most neonatal studies included such measures, although a working group had advised that the course of the disease was similar in adults and children and, thus, that efficacy could be extrapolated with requirements for additional information on pharmacokinetics and safety (Working Group, 2003). Some clinical reviews reported data on activity.

In 2003, the Pediatric Advisory Subcommittee of the Anti-Infective Drugs Advisory Committee discussed the evaluation of antiretroviral drugs in studies with neonates and concluded that FDA should continue to request pharmacokinetic and safety studies for every such drug approved, assuming that the studies were ethical and promised a public health benefit (PAS/AIDAC, 2003). It also advised that decisions about written requests should take into account bioavailability, tolerable toxicity, and the availability of an appropriate formulation.

Studies with Neonates Resulting in No Labeling Change: Bacterial Conjunctivitis

In contrast to the studies of HIV infection, none of the requested neonatal studies of four products for the treatment of bacterial conjunctivitis resulted in the addition of information to product labeling. Clinical reviews and written requests are available for two of these products, moxifloxacin (Vigamox) and gatifloxacin (Zymar), although some information in the reviews is redacted. The written requests were nearly identical. Neither the requests nor the reviews discussed dacryostenosis as a confounding diagnosis or differences in microbiology between conjunctivitis in neonates and older children.

For moxifloxacin (Vigamox), although the clinical review describes a study with neonates (Lim, 2003), the 2003 labeling change merely noted that safety and efficacy had not been established for children less than 1 year of age; it did not include any information from the neonatal study. For gatifloxacin (Zymar), the study of neonates as conducted used moxifloxacin as an active comparator. The reviewer stated that evidence of superiority was expected, but the study showed lower efficacy (i.e., the percentage of subjects whose study eye achieved a score of zero for conjunctival erythema and conjunctival discharge at day 7 of the study was lower) (Nevitt, 2009). The reviewer's summary and risk-benefit assessment were

redacted. Again, no information from the study, for which pediatric exclusivity was granted in 2009, was added to the label.

For the other two products studied with neonates, ciprofloxacin (Ciloxan) and ofloxacin (Ocuflox), FDA has made available only brief summaries of the studies submitted. Both products were granted pediatric exclusivity in 2003 before Congress required that clinical and other reviews and written requests be made public following a grant of exclusivity.[7] For studies that did not lead to a labeling change and for which clinical and other reviews are not available, knowledge is advanced only to the extent that study results are reported—accurately and fully—in the scientific literature. Given concerns about publication bias in industry-sponsored trials, access to the full FDA reviews and redacted text would assist with the evaluation of any published studies.

Although they are not entirely consistent, recent FDA approvals of other products for bacterial conjunctivitis suggest that FDA has changed its views about the nature of this infection in neonates. In each recent case, FDA waived required studies for this age group. For example, in 2010, when FDA approved moxifloxacin hydrochloride (Moxeza) for the treatment of bacterial conjunctivitis in patients 4 months of age and older, it waived pediatric study requirements for ages 0 to 1 month "because the disease does not exist in that age group" (Chambers, 2010, p. 2). (The product is a different formulation of Vigamox, one of the four products discussed above.)

In 2009, in approving besifloxacin ophthalmic suspension (Besivance), a new chemical entity, FDA waived studies with neonates because "ophthalmia neonatorum, a related but different condition, affects children under 1 month of age" (Cox, 2009). Nonetheless, FDA lists a written request as having been issued for besifloxacin (the date and other details are not publically available). In addition, ClinicalTrials.gov (a clinical trials registration database that is described further in Chapter 8) lists a trial registered by the product's sponsor in April 2011 that was recruiting neonates for a randomized, double-blind study to evaluate the safety and efficacy of the product compared to gatifloxacin for treatment of bacterial conjunctivitis (ClinicalTrials.gov identifier: NCT01330355). FDA does not comment on trials under way, but this trial—if related to a written request—would seem to be inconsistent with FDA's recent statements and waivers.

The recent waivers of studies of bacterial conjunctivitis in neonates may reflect recognition of the microbiological and other differences between bacterial conjunctivitis in neonates and older children. Alternatively or in addition, the decisions may reflect the availability of additional pediatric expertise in the review of potential requests or requirements for studies with neonates. Although the details are not available to the committee, this condition was the subject of a consultation with FDA's pediatric ethicists (personal communication, Robert Nelson, Office of Pediatric Therapeutics, FDA, August 10, 2011).

[7] The sponsors refused FDA's request that they allow the clinical and other reviews to be made available to the IOM (personal communication, Catherine Lee, Office of Pediatric Therapeutics, FDA, May 19, 2011, and July 23, 2011). FDA has concluded that the law precludes public disclosure of written requests and FDA reviews when a product had no labeling change and the pediatric studies were conducted and exclusivity was granted before the 2007 reauthorization of BPCA (personal communication, Robert Nelson, Office of Pediatric Therapeutics, FDA, March 31, 2011).

Studies of GERD in Neonates and Changes in Agency Thinking

Like the studies of bacterial conjunctivitis, the requested studies of four proton pump inhibitor (PPI) products for the treatment of GERD in neonates have yielded little labeling information specific to neonates, and studies of PPIs have also not shown it to be effective infants ages 1 month up to 1 year. For older pediatric age groups, requested trials have supported labeling for pediatric use, with the exception of one product (pantoprazole) that was not labeled for use by children up to 5 years of age because of concerns about the formulation used for that age group (Griebel, 2009).

The products for which FDA issued written requests for studies with neonates were omeprazole (Prilosec), lansoprazole (Prevacid), esomeprazole (Nexium), and pantoprazole (Protonix). (The requests also sought studies with older age groups.) The efficacy study for the first of these products included only one neonate (Korvick, 2008); it was excluded by FDA from its table of studies with neonates and was likewise excluded from this analysis. A written request for a fifth product, rabeprazole (Aciphex), is not public, but a pharmacokinetic, pharmacodynamic, and safety trial of this product with newborns is registered at ClinicalTrials.gov and is described as recruiting participants (ClinicalTrials.gov identifier: NCT00855361).

The studies of PPIs in neonates and infants less than 12 months of age illustrate a dilemma for the FDA when clinicians disagree both about the occurrence of GERD in these children and about how to evaluate whether treatment with PPIs is effective (if the condition exists). In 2002, experts in neonatology and pediatric gastroenterology met at a meeting sponsored by the Pediatric Advisory Subcommittee of the Anti-Infective Drugs Advisory Committee but could not agree on how to measure GERD or how to study PPIs in newborns and infants (PAS/AIDAC, 2002). Despite an early lack of agreement among neonatologists and pediatricians about the condition and its treatment, prescriptions for PPIs for infants less than 12 months of age increased fourfold from 1999 to 2004 (Barron et al., 2007).

As early as 1999, FDA concluded that study of the pharmacokinetics and pharmacodynamics of PPIs in all pediatric age groups was appropriate and began to issue written requests for pediatric studies. Pediatric gastroenterologists and FDA staff agreed that GERD in infants was different from the condition in older age groups, so the efficacy of PPIs determined from studies with adults could not be extrapolated to infants (see the discussion of the 2000 symposium on pediatric GERD in Gallo-Torres, 2002). Compared with older infants and children, biopsies of inflamed areas of the esophagus and esophagogastroduodenoscopy are seldom, if ever, used for diagnosis of the condition in newborns. Acid reflux is frequently measured by pH probes in the esophagus, but all babies reflux and spit up to some degree. Moreover, acid reflux is not the same as GERD, although it can lead to GERD. When acid reflux leads to GERD with inflammation and pain, babies cannot report their symptoms. Instead, clinicians or researchers rely on reports from parents (or on investigator observation) of crying, irritability, emesis, arching of the back, and refusal to feed both to diagnose presumed GERD and to measure response to acid suppression.

The committee reviewed written requests for studies of three PPIs to treat GERD in newborns and infants less than 12 months of age. They are nearly identical (for a description of the template, see Gallo-Torres, 2002). The requests were for one study of

pharmacokinetics and pharmacodynamics in neonates and a second study of efficacy.[8] Both types of studies were also to assess safety. The pharmacodynamic and safety component of the first study was specifically to include measures of apnea and bradycardia. Later amendments dropped the requested studies of efficacy in neonates.

The studies with neonates were first requested from 1999 to 2001, and information from the studies was added to the labels in 2008 or 2009, after completion of the studies. The submitted studies did not show a difference in the signs of GERD between neonates who were continued on the drug and neonates who were not. The pharmacodynamic studies showed that the doses used decreased gastric acid production and raised gastric pH. The clinical reviews did not identify unexpected adverse events in neonates, although the reviews did not always specifically describe safety findings for this age group.

Currently, no PPI is labeled as being effective for treatment of neonates or infants less than 12 months of age. Labels do include brief information from the studies with neonates but do not refer specifically to safety findings for this age group. Two labels state that use by children less than 1 year of age is not indicated. One says that the product is not indicated for use by children 1 month to 1 year of age but does not explicitly mention the younger age group (Box 6-2).

BOX 6-2
Current Labeling of PPIs: References to Neonates and Infants

Lansoprazole (Prevacid) (2008 labeling change): "The pharmacokinetics of lansoprazole were studied in pediatric patients with GERD aged *less than 28 days and 1 to 11 months*. Compared to healthy adults receiving 30 mg, *neonates* had higher exposure (mean weight-based normalized AUC [area under the concentration-time curve] values 2.04- and 1.88-fold higher at doses of 0.5 mg/kg/day and 1 mg/kg/day, respectively. *Infants aged ≤ 10 weeks* had clearance and exposure values that were similar to *neonates*. . . . PREVACID was not effective in patients with symptomatic GERD *1 month to less than 1 year of age* in a multicenter, double-blind, placebo controlled study" (emphasis added). (Note that earlier labeling changes had extended the indication from adults to older children.

Pantoprazole (Protonix) (2009 labeling change): "In a population pharmacokinetic analysis, the systemic exposure was higher in patients *less than 1 year of age* with GERD compared to adults who received a single 40 mg dose (geometric mean AUC was 103% higher in preterm *infants and neonates* receiving single dose of 2.5 mg of PROTONIX, and 23% higher *in infants 1 through 11 months of age* receiving a single dose of approximately 1.2 mg/kg). In these patients, the apparent clearance (CL/F) increased with age (median clearance: 0.6 L/hr, range: 0.03 to 3.2 L/hr). These doses resulted in pharmacodynamic effects on gastric but not esophageal pH. Following once daily dosing of 2.5 mg of PROTONIX in *preterm infants and neonates*, there was an increase in the mean gastric pH (from 4.3 at baseline to 5.2 at steady-state) and in the mean % time that gastric pH was > 4 (from 60% at baseline to 80% at steady-state). Following once daily dosing of approximately 1.2 mg/kg of PROTONIX in *infants 1 through 11 months of age*, there was an

[8] In addition to symptom assessments, the initial written requests required measurement of gastric secretion with aspiration of gastric acid every 30 minutes for 6 hours. They also required measurement of the frequency of obstructive apnea; several studies of apnea and reflux show a very low correlation between this measure and other measures of GERD (Peter et al., 2002; Molloy et al., 2005; Mousa et al., 2005; Di Fiore et al., 2010).

increase in the mean gastric pH (from 3.1 at baseline to 4.2 at steady-state) and in the mean % time that gastric pH was > 4 (from 32% at baseline to 60% at steady-state). However, no significant changes were observed in mean intraesophageal pH or % time that esophageal pH was < 4 in either age group. . . . Because PROTONIX was not shown to be effective in the randomized, placebo-controlled study in this age group, the use of PROTONIX for treatment of symptomatic GERD in *infants less than 1 year of age* is not indicated" (emphasis added). (Note that this labeling change extended the indication from adults to individuals aged 5 years and also explained that safety and efficacy were supported for ages 1 up to 5 years but that no suitable formulation was available for patients less than 5 years of age.)

Esomeprazole (Nexium) (2009 labeling change): "The following pharmacokinetic and pharmacodynamic information was obtained in pediatric patients with GERD aged *birth to less than one year of age*. In *neonates (<1 month old)* given NEXIUM 0.5 mg/kg once daily, the percent time with intragastric pH >4 over the 24 hour dosing period increased from 44% at baseline to 83% on Day 7. . . . Apparent clearance (CL/F) increases with age in pediatric patients from *birth to 2 years of age*. . . . Because NEXIUM was not shown to be effective in the randomized, placebo-controlled study for this age group, the use of NEXIUM in patients *less than 1 year of age* is not indicated" (emphasis added). (Note that earlier labeling changes had extended the indication from adult to age 12 years and then to age 1 year.)

A recent review concluded that although these drugs were frequently used, none "has strong evidence for efficacy in decreasing the complications of reflux in preterm infants or term neonates" and, further, that "a few well-conducted, masked, randomized studies that have accounted for maturational changes in their design have raised concerns about the safety of these medications in infants" (Hibbs, 2011, p. e159).

FDA reported that the numbers of new patient prescriptions for all PPIs in the 0- to 1-year-old age group increased from 38,000 in 2002 to 404,000 in 2009 (Murphy, 2010). At a 2010 meeting of the FDA Gastrointestinal Drugs Committee, the focus was mostly on studies of GERD in infants 1 month of age and older. However, the meeting summary states that with respect to neonates, the "committee members remarked that this population is unique and the existing PK [pharmacokinetic] and PD [pharmacodynamic] data are not applicable to this subset" (GIDAC, 2010, p. 6). Some of the comments about older infants are relevant to neonates, for example, comments noting the varied etiology of symptoms and diversity of subpopulations (e.g., infants with cystic fibrosis, erosive esophagitis, or underlying neurological disorders). Continued scientific investigation may help resolve or inform continuing debate about this condition in neonates.

Comment

The studies of drugs for the treatment of HIV infection, bacterial conjunctivitis, and GERD in neonates illustrate situations and factors that appear to promote productive clinical studies, including studies of efficacy, in this age group. Such factors, which were present for the HIV infection studies and absent for the others, include (1) clarity and agreement about the nature of the condition to be studied; (2) valid, reliable, and practical methods to diagnose the condition in neonates and account for the heterogeneity of the population; and (3) valid and reliable endpoints for studies of response or efficacy.

The studies also illustrate how long it can take for requested or required studies to be completed and result in labeling changes that can inform clinical decision making. In the interim, off-label use can become substantial, as has been reported for the PPIs.

Without additional historical analysis, it is difficult to appreciate the extent of relevant knowledge of bacterial conjunctivitis and GERD in neonates at the time that the studies of these conditions were requested and initiated. Nonetheless, greater internal or consulting expertise in neonatal pharmacology and neonatal medicine at FDA might have averted the initiation of some studies of limited value by pointing out issues of toxicity, population heterogeneity, uncertainties about diagnostic criteria, and disagreement about appropriate study endpoints and asking whether a health benefit could be expected from continuing to request such studies.

A 2011 report from the GAO noted criticism that FDA lacked sufficient expertise in the assessment of studies with neonates, particularly neonates who are seriously ill (GAO, 2011). It reported that the PeRC included one neonatologist among its 40 members and that FDA had three other neonatologists in the review divisions at the Center for Biologics Evaluation and Research and the Center for Drug Evaluation and Research, but it did not identify the divisions. Whether additional neonatal expertise would have altered any written requests is unknown.

BPCA, NIH, AND STUDIES WITH NEONATES

Chapters 1 and 3 explained that BPCA created a role for NIH and the Foundation for the NIH in supporting pediatric drug studies for both on-patent and off-patent drugs. If a sponsor declines a written request for a drug that is still on-patent, FDA may refer the request to the Foundation for the NIH. For drugs that are off-patent and that are included in its list of priorities for studies of pediatric therapeutics, NIH may submit a proposal to FDA for a study under BPCA. FDA may issue a written request to all companies that manufacture the product. If all decline, FDA may refer the request to NIH for study.

Table 6-3 lists the written requests issued to NIH that involve studies with neonates. Taken as a whole, the list reflects the importance of antibiotics to treat a range of infections in neonates and, to a lesser extent, the prevalent use of pain medications in this and other pediatric populations.

TABLE 6-3 Written Requests for Neonatal Drug Studies Referred by FDA to NIH, by Patent Status and Study Status

Drug Patent Status and Generic Name (Indication)	Study Performed or Under Way	Request for Neonatal Study Only
Off-patent		
Ampicillin (neonatal sepsis)	None to date	Yes
Azithromycin oral (chlamydia)	No study done	Yes
Azithromycin intravenous (ureaplasma)	Yes	Yes
Lorazepam (sedation)	Yes	No
Meropenem (intra-abdominal infections)	Yes	Yes

Sodium nitroprusside (blood pressure)	Yes	No
Vincristine (cancer)	Yes	No
On-patent		
Morphine intravenous (pain)	Yes	No

SOURCE: Personal communication, Anne Zajicek, Chief, Obstetric and Pediatric Pharmacology Branch, National Institute of Child Health and Human Development, June 29, 2011; see also http://bpca.nichd.nih.gov/clinical/requests/index.cfm).

As part of a BPCA-related Newborn Drug Development Initiative that focused on drugs with no remaining patent term, the National Institute of Child Health and Human Development (NICHD) asked a panel to identify criteria to assist with the setting of priorities for studies with neonates (Giacoia and Mattison, 2005; Ward et al., 2006). In addition to the lack of adequately controlled studies with neonates, the group identified four broad categories of criteria for priority setting, as shown in Box 6-3.

BOX 6-3
Criteria for Selecting Drugs for Priority Investigation in Newborns

Category 1: criteria related to the disease and indication, including the potential for adverse outcomes, frequency in newborns, and level of evidence for treatment of newborns.

Category 2: criteria related to drug characteristics, including elements such as duration of dosing, lack of age-appropriate formulation, clinically relevant drug-drug and drug-disease interactions, and drug disposition in newborns.

Category 3: criteria related to feasibility and methodology for newborn studies, including both analytical considerations and clinical endpoints.

Category 4: criteria related to the ethical basis for study, including the potential benefit or harm due to exposure to the study drug, study methodology, and benefit of the new treatment relative to established standard therapy.

SOURCE: Ward et al. (2006).

In 2011, NICHD published a list of pediatric therapeutic priorities, the latest in a series of such priority lists (NICHD, 2011). For the neonatal group, the list included eight items, all involving studies of medications:

- Betamethasone, azithromycin (intravenous), and hydrochlorothiazide for bronchopulmonary dysplasia. NICHD grants are supporting dosing and efficacy studies of the first two products; the third is the subject of data collection collaboration with the National Heart, Lung, and Blood Institute.
- Morphine for treatment of pain. NICHD is supporting studies of dosing and possible biomarkers.

- Methadone for treatment of opioid-exposed neonates. NICHD is funding multisite pharmacokinetic and safety studies.
- Metronidazole, ampicillin, and meropenem for treatment of neonatal infections. Funding is under consideration for the first two products; the study of the third product is completed and to be submitted to FDA.

As shown above in Table 6-3, FDA has made written requests for studies of three of these products: ampicillin, azithromycin (intravenous), and meropenem. Among other projects supported by NICHD and other units of NIH are studies involving the use of fentanyl, dopamine, and antistaphylococcal antibiotics with neonates (personal communication, Anne Zajicek, Chief, Obstetric and Pediatric Pharmacology Branch, NICHD, June 29, 2011).

CONCLUSIONS

Overall, this report concludes that BPCA and PREA have increased the clinical investigation of drugs in the pediatric population. The committee did not find summary data on studies with neonates before the adoption of these policies but believes, on the basis of experience, that the policies have also led to more studies with neonates than would have occurred without requests under BPCA or requirements under PREA. Nonetheless, by 2010, only 23 labeling changes (not taking into account changes for biologics approved before September 2007) had included information from studies with neonates. Another five products with awards of exclusivity had been studied in neonates, but no information from these studies was added to the labeling.

The committee could not determine how many additional BPCA- or PREA-related studies with neonates were in some stage of planning or execution or had been the subject of NDAs or BLAs for which final determinations had yet to be made. In its report on BPCA and PREA, GAO noted that FDA lacked a formal mechanism for tracking applications through the submission and review process. It recommended the creation of such a system that would, among other features, include information on pediatric studies. If FDA implements such a system, it would be helpful for the system to track pediatric studies by age group, including term and preterm neonates specifically.

Although it is difficult to assess the relevant knowledge base at the time that some of the written requests were issued, the committee had some concerns about whether sufficient expertise in neonatology and neonatal pharmacology was brought to bear on some requests, for example, those for bacterial conjunctivitis and GERD. In requesting or requiring studies with neonates, it is important that FDA consider the extent of use of the drug in this population, the state of current knowledge about the diagnosis in neonates, and the availability of valid and reliable endpoints. In addition, it is important for requests and requirements to be informed by current knowledge of the known and unknown safety profiles of a drug's preservatives and other additives (if any) in neonates.

Resource constraints at FDA are and will be an issue in many areas, including the provision of appropriate, current expertise in pediatrics generally and in neonatology specifically. If, however, the agency is to request or require studies with neonates, it is important that it have sufficient expertise provided by multidisciplinary staff or consultants

to determine the likely health benefit of such studies and to work with sponsors to specify the appropriate safety and efficacy endpoints, inclusion criteria, trial design, and other study elements.

To the extent that many drugs used to treat neonates are old products that have no remaining patent life or exclusivity and that are not the subject of supplemental NDAs or BLAs covered by PREA, the incentives of BPCA and the requirements of BPCA have limited effect. The BPCA program at NIH offers a route for studies of such products with neonates, but proposals for such studies must compete for funding with proposals for studies with other age groups and with proposals considered outside the BPCA program. To date, one study conducted under the auspices of this program has resulted in submission of an NDA, although other studies that may lead to future submissions are under way. Most appear to focus on relatively short-term use, but as noted above, long-term safety studies are also important. *To promote more studies of drugs commonly used but not adequately evaluated in neonates, one option for Congress is to provide additional resources for short- and long-term neonatal drug studies through the BPCA program at NIH.*

Finally, the committee recognizes that long-term studies with any age group are difficult to design, fund, and execute. They are a particular concern with immature and rapidly developing neonates. Although FDA may in some instances request or require that sponsors conduct such studies of neonates, long-term investigations more likely will depend on collaborative efforts that include NIH, FDA, and academic centers. For short-term adverse effects, FDA's postmarket surveillance system may identify problems, as it did with lopinavir-ritonavir (Kaletra), although it cannot be relied upon to do so in a systematic way. If implemented, recommendations to strengthen the system for long-term safety monitoring and assessment could be expected to improve the identification of safety concerns for neonates.

Addendum
Labeling Changes Based on Neonate Studies Requested Under BPCA or Required Under PREA, July 1998 Through December 2010

	Pediatric Labeling Date	Trade Name (Generic or Proper Name)	Indication(s) Studied	Summary of Labeling Change from Studies with Neonates (Excluding Other Changes)	Study Origin	Pediatric Exclusivity Date	Number of Neonates Studied
				Labeling Change for at Least 1 Pediatric Age Group			
1.	12/21/2010	INOmax for inhalation (nitric oxide)	Prevention of bronchopulmonary dysplasia (BPD)	INOmax is not indicated for prevention of BPD in preterm neonates ≤34 weeks of gestational age. Efficacy for the prevention of BPD in preterm infants was not established in three double-blind, placebo-controlled clinical trials with a total of 2,149 preterm infants. Information on clinical trials, adverse reactions.	BPCA	11/2/2010	Three trials with 800, 587, and 793 neonates
2.	11/2/2010	Ofirmev injection (acetaminophen)	Management of mild to moderate pain, management of moderate to severe pain with adjunctive opioid analgesics, and reduction of fever	The effectiveness of Ofirmev for the treatment of acute pain and fever has not been studied in pediatric patients <2 years of age. The PKs of exposure to Ofirmev observed in children and adolescents is similar to that observed in adults but is higher in neonates and infants. Dosing simulations from PK data for infants and neonates suggest that dose reductions of 33% in infants 1 month to <2 years of age and 50% in neonates up to 28 days of age, with a minimum dosing interval of 6 hours, will produce a PK exposure similar to that observed in children age 2 years and older. Safety and PK data, dosing, and AE information.	PREA	NA	47
3.	11/12/2009	Protonix (pantoprazole)	GERD	Effectiveness was not demonstrated in a clinical trial of patients 1 month to 11 months of age with symptomatic GERD. Information on PK, PD in neonates.	BPCA, PREA	2/17/2009	68 neonates enrolled; 59 randomized
4.	8/28/2009	Valcyte (valganciclovir)	Prevention of cytomegalovirus (CMV) disease in pediatric kidney and heart transplant patients	Efficacy and safety for prevention of CMV disease after solid organ transplant have not been established in patients <4 months of age. Information on PK, PD in neonates.	BPCA, PREA	7/24/2008	24

	Pediatric Labeling Date	Trade Name (Generic or Proper Name)	Indication(s) Studied	Summary of Labeling Change from Studies with Neonates (Excluding Other Changes)	Study Origin	Pediatric Exclusivity Date	Number of Neonates Studied
5.	6/18/2009	Nexium (esomeprazole)	Short-term treatment of GERD	Effectiveness was not demonstrated in a randomized, placebo-controlled study with neonates to <1 year. Information on clinical study and PK/PD parameters in neonates is included in the label.	BPCA, PREA	5/1/2009	26
6.	10/28/2008	Prevacid (lansoprazole)	Symptomatic GERD in infants	Safety and effectiveness have not been established in pediatric patients <1 year of age. Information about neonatal clinical trial, PK, safety.	BPCA, PREA	7/15/2008	24
7.	8/28/2008	Zemuron (rocuronium)	Adjunct to general anesthesia	Expanded pediatric indication to include children ages 0 to 17 years. Previously approved for by use by infants ages 3 months to 14 years. The time to maximum block for an intubating dose was shortest in infants and longest in neonates. The duration of clinical relaxation following an intubating dose is shortest in children ages >2 years to 11 years and longest in infants. Additional information on safety, dose, PK/PD parameters, and other details.	BPCA, PREA	4/3/2008	18 ITT for study 1; 10 ITT for study 2
8.	7/29/2008	Cancidas (caspofungin)	Empirical therapy for presumed fungal infections in febrile, neutropenic patients; candidemia and certain *Candida* infections; esophageal candidiasis; and invasive aspergillosis in patients who are refractory to or intolerant of other therapies	The efficacy and safety of Cancidas have not been adequately studied in prospective clinical trials involving neonates and infants less than 3 months of age. Although limited PK data were collected from neonates and infants less than 3 months of age, these data are insufficient to establish a safe and effective dose of caspofungin for the treatment of neonatal candidiasis. Invasive candidiasis has a higher rate of CNS and multiorgan involvement in neonates than in older patients.	BPCA, PREA	4/15/2008	18
9.	6/24/2008	Viramune tablets, 200 mg Viramune oral suspension, 10 mg/mL (nevirapine)	Use in combination with other antiretroviral agents for the treatment of HIV-1 infection	Dosing information provided for children ages >15 days to <16 years. Safety was evaluated in children ages 2 weeks and older in five clinical trials. Important adverse events (all causality) include rash (21%), neutropenia (8.9%), anemia (7.3%), and hepatotoxicity (2.4%). Safety and pharmacokinetics were evaluated in HIV-infected pediatric patients ages 15 days to <3 months.	PREA	NA	Not specified

	Pediatric Labeling Date	Trade Name (Generic or Proper Name)	Indication(s) Studied	Summary of Labeling Change from Studies with Neonates (Excluding Other Changes)	Study Origin	Pediatric Exclusivity Date	Number of Neonates Studied
10.	6/20/2008	Kaletra (lopinavir/ ritonavir)	Use in combination with other antiretroviral agents for HIV-1 infection	The safety, efficacy, and PK profiles have not been established in pediatric patients <14 days. Dose should be calculated on the basis of body weight or BSA so that it does not exceed the adult dose. Infants <6 months of age generally had lower lopinavir AUC_{12} values than children 6 months to 12 years of age. Other information on clinical studies and AEs.	BPCA, PREA	3/7/2008	Not specified
11.	12/27/2007	Voluven (6% hydroxyethyl starch 130/0.4 in 0.9% sodium chloride injection)	Plasma volume substitute for treatment and prophylaxis of hypovolemia	Limited clinical data on the use of Voluven in children are available. In 41 children, including newborns to infants (<2 years), a mean dose of 16 ± 9 mL/kg of body weight was administered. The dosage in children should be adapted to the individual patient's colloid needs, taking into account the disease state, as well as the hemodynamic and hydration status.	PREA	NA	Not specified
12.	12/22/2006	Emtriva (emtricitabine)	HIV-1 infection in combination with other antiretroviral agents	Efficacy in preventing or treating HIV infection in neonates to age 3 months could not be determined after a PK study with 20 neonates born to HIV-positive mothers . Information on dose in neonates 0 to 3 months of age, additional safety and PK parameters.	BPCA	5/24/2006	22
13.	5/12/2005	Zyvox (linezolid)	CNS infections	Use of linezolid for the empirical treatment of pediatric patients with CNS infections is not recommended. Additional information on efficacy in pediatric patients with infectious vancomycin-resistant *Enterococcus faecium* is provided. PK studies, dosage, AE.	BPCA	2/11/2005	42 completed
14.	4/1/2004	Corlopam (fenoldopam)	Indicated for in-hospital, short-term reduction in blood pressure	Indicated for in-hospital, short-term (up to 4 hours) reduction in blood pressure in pediatric patients ages <1 month (weight at least 2 kg) to 12 years.	BPCA	NA	At least 2
15.	3/19/2004	Viracept (nelfinavir)	HIV-1 infection	A reliably effective dose was not established for patients <2 years of age. Two studies with infants less than 12 weeks old looking at PK and safety.	BPCA, PREA	9/4/2003	31
16.	3/8/2004	Ultiva (remifentanil)	Maintenance of anesthesia	Safety and efficacy for the maintenance of anesthesia were established for patients from birth to 1 year	BPCA, PREA	3/15/2000	8 in PK study; other

	Pediatric Labeling Date	Trade Name (Generic or Proper Name)	Indication(s) Studied	Summary of Labeling Change from Studies with Neonates (Excluding Other Changes)	Study Origin	Pediatric Exclusivity Date	Number of Neonates Studied
				of age. Recommended dosing guidelines for maintenance of anesthesia were established for patients from birth to age 2 months. The clearance rate observed in neonates was highly variable: approximately two times higher than that in young healthy adults.			not specified
17.	4/15/2003	Vigamox (moxifloxacin)	Bacterial conjunctivitis	None specifically from studies with neonates.	BPCA	1/10/2003	209
18.	10/8/2002	Epivir (lamivudine)	HIV infection	Lamivudine clearance was substantially reduced in 1-week-old neonates relative to pediatric patients >3 months of age. Two safety and PK trials with neonates and some information on AE.	BPCA	9/22/2000	Not specified
19.	6/6/2002	Pepcid (famotidine)	Gastroesophageal reflux disease	Labeling for patients less than 1 year of age was provided, including information on dose, PK/PD parameters, and AE profile. Lower dose recommended in patients <3 months of age. Some data on PK and dosing studies with neonates.	BPCA	11/21/2000	10
20.	4/1/2002	Videx (didanosine)	HIV infection	Safety and effectiveness were established down to 2 weeks of age. Dosing information for children between 2 weeks and 8 months of age.	BPCA	8/13/2001	8.
21.	3/29/2002	Zerit (stavudine)	HIV infection	Safety and effectiveness were established down to birth. A dose for newborns from birth to 13 days was established. Description of clinical trial with newborns.	BPCA	8/13/2001	8
22.	10/1/2001	Betapace (sotalol)	Arrhythmia	Analysis of two trials provided information on PK and PD in children ages 3 days to 12 years; safety and efficacy not established. Information on dose. Pharmacokinetics: BSA was the most important covariate and more relevant than age. Smaller children (BSA < 0.33 m^2) showed a tendency for larger change in QTc interval and increased frequency of prolongation of the QTc interval as	BPCA	1/6/2000	2 (study 1) 7 (study 2)

	Pediatric Labeling Date	Trade Name (Generic or Proper Name)	Indication(s) Studied	Summary of Labeling Change from Studies with Neonates (Excluding Other Changes)	Study Origin	Pediatric Exclusivity Date	Number of Neonates Studied
				well as greater beta-blocking effects. Individualized dosing on a mg/m^2 basis.			
23.	3/30/2001	Ultane (sevoflurane)	Induction and maintenance of general anesthesia	New study with pediatric patients ages 9 days to 12 years compared sevoflurane and halothane. No specific data for neonates in the clinical trial information.	BPCA	8/2/2000	At least 3
24.	10/22/1999	Zantac (ranitidine)	Gastroesophageal reflux	Small studies with newborns ages 0 to 1 month receiving ECMO did not demonstrate efficacy but provided information on dose and PK.	BPCA	1/19/1999	12
				No Labeling Change for Any Age Group			
25.	NA	Angiomax (bivalirudin)	Anticoagulant in pediatric patients during percutaneous intravascular procedures for management of congenital heart disease	None	BPCA	6/17/2009	10
26.	NA	Zymar (gatifloxacin)	Bacterial conjunctivitis	None	BPCA	5/19/2009	171
27.	NA	Ciloxan (ciprofloxacin)	Bacterial conjunctivitis	None	BPCA	1/10/2003	209
28.	NA	Ocuflox (ofloxacin)	Bacterial conjunctivitis	None	BPCA	3/12/2003	173

NOTES: Twenty-eight products were evaluated: 23 with labeling change and 5 with no labeling change related to studies with neonates. Abbreviations: B = BPCA; P = PREA; R = Pediatric Rule; PK = pharmacokinetics; PD = pharmacodynamics; AE = adverse events; ITT = intent to treat; NA = not applicable; AUC_{12} = area under the concentration-time curve from time zero to 12 h; CNS = central nervous system; BSA = body surface area; ECMO = extracorporeal membrane oxygenation.
SOURCE: Summarized from a compilation supplied by FDA. Except for the last four products listed, most of the information is taken from a table accessible online at http://www.fda.gov/downloads/ScienceResearch/SpecialTopics/PediatricTherapeuticsResearch/UCM163159.pdf. Data on number of neonates studied is from the product's label or from posted FDA summary reviews (2003 to 2008) or FDA clinical or clinical pharmacology reviews (from September 27, 2007).

7
Outcomes of Written Requests, Requirements, Studies, and Labeling Changes

One measure of the accomplishments that have been achieved under the Best Pharmaceuticals with Children Act (BPCA) and the Pediatric Research Equity Act (PREA) is simply the number of labeling changes attributed to these policies since they or their predecessor policies went into effect. From July 1, 1998, through October 25, 2011, the Food and Drug Administration (FDA) approved 425 labeling changes as a result of studies or analyses requested under BPCA or required under PREA.[1] FDA attributed approximately half (54 percent) of the changes to studies required under PREA and approximately one third (35 percent) to studies requested under BPCA; the remaining changes (11 percent) were attributed to both laws.[2]Almost 10 percent (n = 39) of the changes were not based on data from new pediatric studies. For example, for a 2009 change in pediatric dosing for zidovudine (Retrovir) for the treatment of HIV infection, FDA approved the change on the basis of the sponsor's reanalysis of existing data (Alivisatos, 2008).

As noted elsewhere in this report, FDA's listings of labeling changes related to BCPA and PREA (and their predecessor policies) are not complete. Specifically, they do not include changes for some biologics that were made prior to September 27, 2007. FDA could not supply the committee with the missing information. Thus, the list provided to the committee understates to an unknown extent the number of labeling changes made as a result of studies of biologics that were required under PREA.

Figure 7-1 shows the time trend of labeling changes attributed by FDA to BPCA and PREA through October 25, 2011. From 1998 through 2004, the general pattern is one of yearly increases in the number of changes attributable to BPCA. Although the pattern after that is uneven, most subsequent years show a decrease in changes attributable to BPCA alone. Since 2005, pediatric studies required under PREA have accounted for most

[1] One further labeling change was posted for December 2011, and as of the end of January 2012, FDA indicated that eight more changes were yet to be posted (personal communication, Catherine Lee, Office of Pediatric Therapeutics, FDA, January 27, 2012). The first labeling change in FDA's listing (February 10, 1998 for naratriptan [Amerge]) is attributed to the 1994 Pediatric Rule (personal communication, Robert Nelson, Office of Pediatric Therapeutics, FDA, January 10, 2011).

[2] Some products have more than one labeling change (e.g., for different indications or additional pediatric age groups. A labeling change can involve either the addition of pediatric information to the existing label for a previously approved product or the new labeling of a product not previously approved.

labeling changes. Some of these changes are for products studied from the outset in at *least one pediatric age group.*

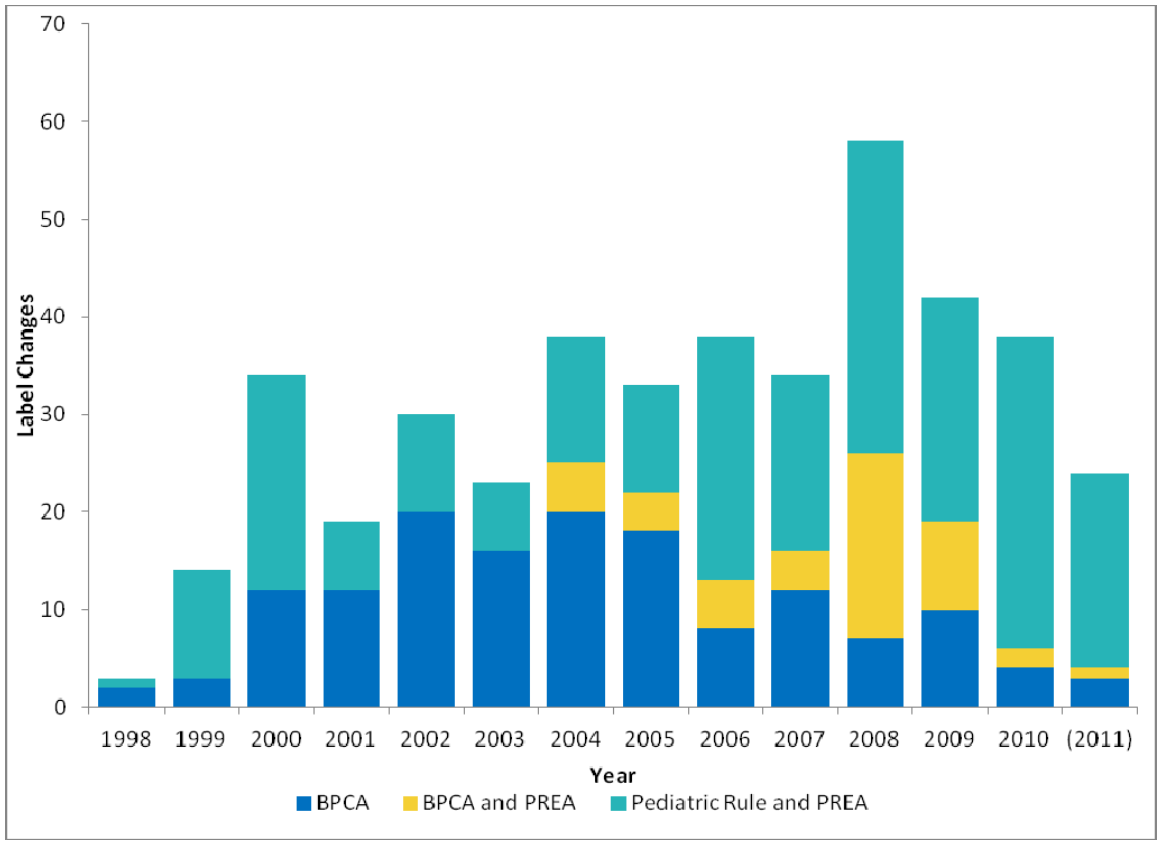

FIGURE 7-1 Changes in drug labeling associated with BPCA, PREA (including the Pediatric Rule), or both, July 1998 through October 2011. The figure excludes changes for some biologics regulated under the Public Health Service Act that were approved before September 27, 2007. It includes changes for some products (e.g., contraceptives) that were excluded from the committee's analysis as well as one change that is attributed to the 1994 Pediatric Rule.
SOURCE: Compiled from information periodically updated in an Excel file downloadable at http://www.accessdata.fda.gov/scripts/sda/sdNavigation.cfm?sd=labelingdatabase

A few labeling changes that are attributed to PREA might be more appropriately linked to other policies. One such policy is FDA's unapproved drugs initiative (FDA, 2006a). That initiative has led to pediatric studies and the approval of three previously unapproved but long-marketed pancreatic enzyme replacement products for use by children and adults (see, e.g., Giuliano et al., 2011). When it approved each product, FDA imposed a deferred PREA requirement for the development of a formulation suitable for the youngest and lowest-weight patients (see, e.g., Beitz, 2009a).

To cite a different example, the labeling of pralidoxime chloride (Protopam) for pediatric use in 2010 (attributed to PREA, with no new studies submitted) might be

credited to efforts of the child health advocates and others concerned about children's access in emergencies to this treatment for exposure to organophosphate pesticides and chemicals (e.g., nerve agents) (Krug et al., 2011). The drug was originally approved in 1964 and was listed by the National Institute of Child Health and Human Development as a priority for a systematic literature review in 2006 (71 FR 23931). The 2011 to 2016 strategic plan of the Biomedical Advanced Research and Development Authority (a unit with the Department of Health and Human Services) includes "supporting the development of medical countermeasures suitable for use in special populations such as children" (BARDA, 2011, p. 11).

Some pediatric studies conducted and submitted to FDA under BPCA have not yielded labeling changes. With its list of products with labeling changes related to BPCA and PREA, FDA also supplied the committee with a list of 14 active moieties for which requested studies were conducted and exclusivity was granted without information from the studies being added to the label. In addition, it is possible that some requests have led to studies for which FDA neither approved a labeling change nor granted exclusivity. FDA may deny exclusivity if submitted studies do not meet the terms of the written request.

Twelve of the 14 grants of exclusivity without labeling changes were approved before September 2007. For five of these, no information about the study results is posted. For the remaining seven, short summaries are available (consistent with the requirements of BPCA of 2002). Some of these summaries reveal that FDA concluded that no labeling change was necessary because the studies had not demonstrated efficacy but did not raise new safety signals. In one case, a summary reveals FDA's concern that inclusion of any information from a requested study (of the pharmacokinetics of topotecan [Hycamtin]) could be interpreted to imply approval for pediatric use even if the label noted that safety and efficacy had not been established (Hirschfeld, 2003).

In addition, in a presentation to the Institute of Medicine (IOM) committee, FDA staff explained that in the early years of BPCA and PREA (and the Pediatric Rule), pediatric studies were sometimes submitted in sponsor's annual reports (not as part of New Drug Application [NDA] or Biologics License Application [BLA] submissions), were not reviewed, and did not lead to labeling changes (Mathis and Jain, 2011). Moreover, the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER) traditionally did not amend labels to reflect efficacy findings that did not support pediatric use. For example, the labeling for fluconazole (Diflucan) still does not note that the product was studied (by request) for the treatment of tinea capitis in children and that the studies found that the product did not work better than an already approved product (griseofulvin) (Mathis and Jain, 2011).

In the Food and Drug Administration Amendments Act of 2007 (FDAAA), Congress required that information from studies conducted under PREA and BPCA be incorporated in the labeling, whether or not they supported pediatric use or raised new safety signals. Congress also directed that FDA post the clinical, clinical pharmacology, and statistical reviews for these studies. Both actions increased the value to the public of the studies requested under BPCA or required under PREA.

Nevertheless, two products (bivalirudin [Angiomax] and gatifloxacin [Zymar]) that were granted exclusivity after the passage of FDAAA did not have associated labeling changes. The clinical reviews for these products are posted, but the

recommendations on regulatory action and all or part of the risk-benefit assessments are redacted (Ayache, 2009; Nevitt, 2009), making it difficult to assess why no labeling change was made.

The rest of this chapter starts with a discussion of written requests and PREA requirements, including those covered in the committee's sample. Later sections discuss the committee's assessment of pediatric studies (as reviewed by FDA staff) and labeling changes. (Appendix A discusses how the committee selected its sample.)

WRITTEN REQUESTS AND PREA REQUIREMENTS

Written Requests

Status of Written Requests

By October 2011, FDA had issued 340 written requests since BPCA became effective on July 1, 1998.[3] Of these requests, FDA had subsequently granted exclusivity for 176 active moieties (and 185 products).[4] Thus, roughly half of the written requests issued to date have led to the submission of pediatric studies for which exclusivity was granted, although at least 14 of these did not lead to changes in product labeling. Although FDA does not identify them, some written requests have been declined by sponsors and other requests are still open, with studies planned, under way, or submitted but not yet evaluated. Some sponsors have submitted some of the requested studies, but an exclusivity determination will not be made until all the requested studies are submitted and evaluated. More grants of exclusivity and labeling changes can be expected for previously issued written requests.

Figure 7-2 shows trends in the issuing of written requests and the granting of exclusivity. Written requests peaked in 1999 and then dropped off sharply, with a relative leveling off more recently. Although FDA sometimes issues written requests for studies that are under way or already completed (see discussion of nitric oxide in Chapter 6), studies initiated in response to written requests usually take years to plan, conduct, complete, analyze, and submit. Thus, the peak in grants of exclusivity comes in 2008, several years after the peak for written requests.

[3] Unless otherwise noted, the data discussed in this section are compiled from FDA sources. The agency lists the moieties for which requests have been made and posts statistics on written requests and exclusivity at http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm.

[4] Of the 138 earliest written requests that were issued as of September 2000 (Appendix B in FDA, 2001), FDA had approved labeling changes for 78 (56 percent) of the active moieties by October 2011. Some of these written requests may still be open. For example, in 2010, an FDA advisory committee was asked for its views on the advisability of an amendment to a 2001 written request for studies of the drug sildenafil (Revatio) for treatment of pulmonary arterial hypertension (Temple, 2010).

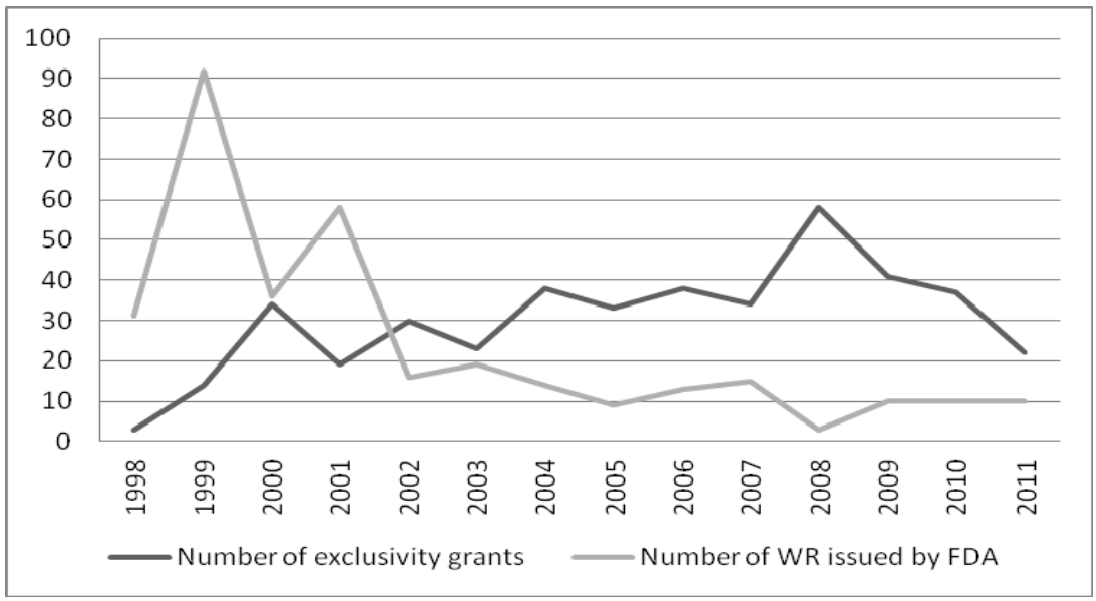

FIGURE 7-2 Number of written requests (WR) issued and number of grants of exclusivity, by year, July 1998 through September 2011.
SOURCE: Personal communication, Catherine Lee, Office of Pediatric Therapeutics, FDA, November 3, 2011.

The early surge in written requests is not surprising, given that neither incentives nor requirements for pediatric studies had previously been in place and that a substantial number of already approved drugs had not been studied in children (see Table 1-1 in Chapter 1). Once FDA had issued requests for many obvious candidates (e.g., drugs widely used off-label by children, blockbuster drugs with possible pediatric use, and drugs with pediatric studies already planned or under way), a subsequent decline is not surprising. Also, with the passage of time, a reduction in requests could be expected in part because of the growth in the number of products for which studies had been required under PREA and in part because of the loss of eligibility for popular older products as existing patents or other exclusivity expired.

Despite its declining role, BPCA has continuing value because its incentives are not limited to the indications covered by an application for the approval of a new drug. For example, written requests may take into account advances in knowledge since a determination about required studies of an indication was made under PREA. New data may show that a condition is more common in children than previously believed or new research may suggest a promising new use in children.

Most written requests are proposed by sponsors rather than initiated by FDA, although FDA may significantly alter those proposals. Overall, sponsor proposals are associated with approximately 80 percent of the written requests that FDA had issued as of October 31, 2011. FDA initiated the other 20 percent of requests. By October 2011, FDA had received approximately 700 sponsor proposals for written requests. The high rate of requests related to sponsor proposals may explain why almost 90 percent of written requests issued since January 1, 2008, have been accepted by sponsors (personal

communication, Catherine Lee, Office of Pediatric Therapeutics, FDA, November 30, 2011).

Changes in Written Requests

The committee's sample of 46 FDA actions included 27 products for which written requests were issued, including one product for which the written request covered two indications. Some requests were not amended; others had four or more amendments. The committee (or consultants) also reviewed additional written requests for studies of migraine, hypertension, and gastroesophageal reflux disease (GERD). Most of these additional requests and any amendments dated from the late 1990s to the mid-2000s and thus were not reviewed by the Pediatric Review Committee (PeRC), as provided for in the reauthorization of BPCA in 2007 (see Chapter 3).

The requests that the committee reviewed generally followed a standard template similar to the one presented in Chapter 3. Depending on the drug and indication, FDA might also have developed a more substantive, product-specific template. It has done so, for example, for studies of pediatric hypertension, migraine in adolescents, and GERD. Box 7-1 summarizes major substantive changes in written requests for studies of migraine. Chapter 6 summarizes the changes in written requests for studies of proton pump inhibitors to treat GERD in neonates and infants, and Appendix E provides a more detailed analysis of changes in written requests for studies of pediatric hypertension.

BOX 7-1
Major Amendments to Written Requests for Pediatric Studies of Drugs for Treatment of Migraine

Zolmitriptan (Zomig)
The written request for zolmitriptan was issued in March 1999. It specified four studies: (1) a short-term safety and tolerability study (sample size not specified), (2) a pharmacokinetic study (sample size not specified), (3) a well-powered efficacy study (sample size not specified), and (4) a long-term safety study with 300 subjects. There were no amendments.

Sumatriptan (Imitrex)
The original written request for sumatriptan was issued in June 1999. It specified three studies: (1) a single-dose pharmacokinetic study with adolescents (sample size not specified), (2) a well-powered efficacy study (sample size not specified), and (3) a long-term safety study with 300 subjects. The amended written request in May 2000 changed the entry criteria in the efficacy and safety studies from subjects with an average of one to six migraines per month (with "migraines" defined by the International Headache Society) to subjects with an average of two or more migraines per month, as requested by the sponsor. The amendments also allowed the sponsor to compare pharmacokinetic results from adolescents with those from historical adult controls.

Almotriptan (Axert)
The original written request for almotriptan was issued in October 2001. It specified the need for three studies: (1) a single-dose pharmacokinetic study with 18 to 50 adolescents, (2) a well-powered efficacy study (sample size not specified), and (3) a long-term safety study with 300

adolescents. The amended written request in February 2005 dropped the request for the pharmacokinetic study and decreased the sample size of the third study to 200 participants. Inclusion criteria for the efficacy trial did not change between the original and the amended request.

Eletriptan (Relpax)
The written request for eletriptan was issued in July 2004. It specified two studies: (1) a well-powered efficacy study (specific sample size not specified) and (2) a long-term safety study with 200 adolescents. There were no amendments. (Note that in August 2005 this written request was referred to the Foundation of the National Institutes of Health in accord with provisions of BPCA of 2002 [71 FR 6081; see Chapter 3 for a discussion of these provisions].)

SOURCE: Personal communication, P. Brian Smith, Department of Pediatrics, Duke University Medical Center, June 22, 2011.

The substantive details in written requests have tended to become somewhat more specific over time. Changes in the basic request template or in specific requests have often

- added precision (e.g., by specifying a period for safety follow-up or a minimum percentage for age or racial subgroups in a sample);
- required more rigor in trial designs (e.g., by dropping the option for a trial with no placebo and only alternative doses of the test drug or by increasing the statistical power of trials to detect a clinically meaningful effect);
- required more accommodation of developmental variability (e.g., by requiring sponsors to try to develop age-appropriate formulations, if needed); or
- incorporated the legislative requirements for greater public access to information about study results (e.g., by requiring that sponsors submit NDA supplements to add information from trials—whether negative or positive—to the label.

Although FDA's letters that describe amendments in particular written requests often do not explain the reason for changes, subsequent clinical reviews of submitted studies suggest that some changes have come after a sponsor encountered difficulties with conducting the studies as requested. For example, if studies with an older age group identified serious safety concerns (e.g., as in studies of the anesthetic desflurane), the agency might amend a request to eliminate a study with a younger age group. Similarly, if a sponsor encountered serious difficulties in enrolling children, an amendment might reduce the specified small size.

Potential of Requests to Generate Useful Information

On the basis of the requests in its sample, the committee concluded that most written requests had reasonable potential to generate useful information for clinicians who care for children. These include requests for studies of drugs that

- had a new mechanism of action compared with existing medications approved for pediatric use (e.g., aripiprazole for schizophrenia) or were improvements over first-generation drugs in the class (e.g., many second- or later-generation antibiotics);
- offered a possible treatment for a serious or life-threatening condition for which few or no treatments had been demonstrated to be safe and effective (e.g., irinotecan hydrochloride for treatment of solid tumors and bisphosphonates for treatment of osteogenesis imperfecta);
- were commonly used off-label with no controlled studies of pharmacokinetics, dosing, safety, or efficacy (e.g., antibiotics for various infections and proton pump inhibitors for GERD);
- lacked important information on safety (e.g., desflurane for the maintenance of anesthesia in nonintubated children);
- would potentially allow safe and effective use of the drug in a new pediatric population if a new formulation was developed (e.g., terbinafine hydrochloride for tinea capitis); or
- had new safety concerns suggested by new data (e.g., remifentanyl hydrochloride for anesthesia).

Some requests had elements that, in the committee's judgment, could limit the potential of the requested studies to yield strong information to guide the care of children. Box 7-2 provides examples.

BOX 7-2
Elements in Written Requests That Could Limit the Potential of Studies to Yield Useful Information

Toxicity profile of drug. One request involved a drug (stavudine [Zerit]) with a known toxicity profile that made its use for HIV-exposed or -infected neonates or young infants unlikely given available alternative treatments.

Timing of pharmacokinetic study. For a drug (levalbuterol tartrate [Xopenex HFA]) to treat asthma, a request did not specify that pharmacokinetic studies be performed early enough to guide the efficacy and safety trial.

Failure to request pharmacokinetic study. FDA requested safety and efficacy studies but not a pharmacokinetic study for a drug to treat asthma (albuterol sulfate inhalation aerosol [Ventolin HFA]) in children ages birth up to 2 years and 2 years up to 4 years. The clinical reviewer concluded that the studies did not show efficacy and that the dose chosen for the studies might not have been optimal (Wang, 2008).

Failure to request relevant studies. For a drug (inhaled nitric oxide [INOmax]) to prevent bronchopulmonary dysplasia in newborns, FDA did not request pharmacokinetic data, despite the diverse gestational ages of infants to be studied, and did not specify safety endpoints other than those associated with prematurity.

Need to tailor studies to age groups. As specified in a request for studies of esomeprazole magnesium [Nexium]), a study design with a run-in treatment stage followed by randomized,

placebo-controlled withdrawal, although appropriate for older age groups, may not be optimal in a study of the treatment of GERD in infants. If the initial run-in phase effectively heals erosive esophagitis, withdrawal is not likely to show a significant difference between the placebo treatment and the proton pump inhibitor treatment. An amendment to the written request eliminated the efficacy study, although the drug is widely used by infants.

Selection of endpoints inappropriate for age group. In a study of a drug (salmeterol xinafoate/fluticasone propionate [Advair]) for treatment of asthma in children ages 4 to 11 years, the requested endpoint of forced expiratory volume in 1 second (FEV1) did not adequately recognize the inability of the youngest children to perform the necessary breathing maneuvers.

Insufficient definition or scope of intervention. For a requested study of an anesthetic agent (desflurane [Suprane]), the request specified management by either a face mask or a laryngeal mask airway device, leaving the choice of approach to the anesthesiologist rather than defined as part of the trial design.

To focus on one therapeutic area, details of the written requests for pediatric studies of a number of drugs used to treat hypertension in adults—and the resulting trials—have been criticized for a number of reasons. An analysis by Benjamin and colleagues reached the following conclusions:

> Successful studies showed large differences in doses, with little or no overlap between low, medium, and high doses; failed trials used narrow dose ranges with considerable overlap. Successful trials also provided pediatric formulations and used reduction in diastolic, not systolic, blood pressure as the primary endpoint. Careful attention to pediatric pharmacology and selection of primary endpoints can improve trial performance. We found poor dose selection, lack of acknowledgment of differences between adult and pediatric populations, and lack of pediatric formulations to be associated with failures. (Benjamin et al., 2008, p. 834)

The authors have also suggested that for these trials feasibility was more important to the sponsors than strong trial design, particularly since exclusivity can be granted regardless of whether studies demonstrate efficacy. As noted in Appendix E, FDA has amended the template for requests for these studies by specifying stronger trial design options, which are more likely to provide useful information about efficacy.

As described in Chapter 6, some requests for studies with neonates yielded little information, in part because of uncertainty about the nature and means of assessment of the condition in children. At the same time, the chapter noted the shortage of studies of drugs often prescribed off-label for neonates. In addition, certain categories of requests, for example, repeated requests for studies of similar ("me too") drugs, were generally not compelling, although studies of such drugs might still provide some useful pharmacokinetic and dosing information. For the variety of drugs used for the treatment of AIDS, often in new combinations, pediatric studies (sometimes requested, sometimes required) provide reassurance about safety and appropriate dosing in children.

Except for sponsors, who may propose pediatric study requests, no organized process currently exists to obtain broader public input. Moreover, neither Congress nor

FDA has spelled out the criteria to be considered in assessments of the health benefits of a request, and written requests usually contain little or nothing by way of rationale for the request. It is not clear that the magnitude or importance of the expected benefit matters. Particularly for requests that follow several other requests for studies of drugs in the same class, especially when the initially requested studies do not find efficacy, it would be in the public interest for FDA to discuss whether the expected benefit of a drug proposed for a written request would exceed that of existing therapies for all or some subgroups of children (e.g., because the drug allowed less frequent dosing or had a safer formulation).

In addition, although it did not consider alternatives to the current period of exclusivity, the committee was troubled by the disparity in effort associated with more demanding requested studies that lead to the same reward as less demanding studies. Six months of exclusivity is the reward whether the requested studies primarily involve small pharmacokinetic, pharmacodynamic, and safety studies or larger, well-controlled studies of safety and efficacy. These concerns do not imply the need to change the current policy that allows the granting of exclusivity for both studies with positive results and studies with negative results, as long as they meet the terms of the written request.

The committee concluded that, in general, changes in the basic template for written requests and the amendments to specific written requests have improved requests. Although the committee examined few written requests that were issued after the PeRC initiated its reviews and many of these requests are not yet public, it expects that the additional pediatric and methodologic expertise provided by these reviews are improving the quality of requests (and subsequent studies). As described in Chapter 6, the lack of availability of expertise in neonatal research and clinical care, including for the specification of appropriate written requests for studies of the youngest pediatric patients, remains a concern.

Written Requests and NIH

As explained in Chapter 3, BPCA of 2002 created a role for the National Institutes of Health (NIH) and the Foundation for the NIH in supporting pediatric drug studies for both on-patent and off-patent drugs. The Government Accountability Office (GAO) has reported that one sponsor accepted a written request for study of an off-patent drug between 2002 and the end of 2005 (GAO, 2007). No sponsor has accepted a written request for an off-patent drug since then (GAO, 2011).

According to the director of BPCA activities at the National Institute of Child Health and Human Development (NICHD), FDA has referred to NIH 9 written requests for studies of on-patent drugs and 17 requests for studies of off-patent drugs (involving 14 products) (personal communication, Anne Zajicek, Chief, Obstetric and Pediatric Pharmacology Branch, NICHD, June 29, 2011, and December 1, 2011).[5] It has referred. The results of at least five NIH-funded studies have been submitted to FDA.

Application of PREA Requirements

[5] The requests are posted at http://bpca.nichd.nih.gov/clinical/requests/index.cfm.

As described above, PREA requirements have become increasingly important as a source of pediatric studies. As noted earlier, the scope of such requirements is limited to the indication covered in a New Drug Application (NDA) or BLA submission. Nonetheless, even when a required study is limited to only the most recent of several indications for which the product has been approved for adults, a pediatric study of use of the drug for that indication may increase understanding of the drug's pharmacokinetics and safety profile and thereby provide information relevant to off-label use for other indications.

To help understand how FDA specified requirements for pediatric studies, the committee examined, when possible, the FDA letters to sponsors that originally set forth requirements. The committee also reviewed some approvals letters for biologics, as will be discussed in Chapter 8. In addition, to get a sense of how FDA is now applying PREA requirements, the committee examined several approval letters issued in 2011.

In some cases, the committee found approval letters (mostly issued several years ago) that did not mention the requirement for pediatric studies. In some cases, that was an oversight, and studies were required. In other cases, the sponsor had an orphan drug designation for the product or an indication in question or FDA did not consider the submission to involve a new active ingredient, indication, new dosage form, new dosing regimen, or new route of administration.[6] The lack of explicit discussion of PREA requirements is, nonetheless, an oversight.

One difficulty for the committee and others seeking to assess activities performed under PREA is that the FDA has no easily used, comprehensive public database of product-specific PREA requirements covering the period from the Pediatric Rule to the present. (As described below, the agency does have a website that allows searches for studies required under PREA.) It sometimes required examination of several sources to identify FDA's determinations about waivers or deferrals of PREA requirements for particular products, and information for biologics was sometimes lacking altogether.

Rationales for Waived or Deferred Studies

With respect to PREA requirements stated in FDA letters, the committee concluded that statements about waivers or deferrals have become more specific and somewhat more informative to the public over time. Some early letters did not mention requirements of the Pediatric Rule or merely noted that required studies had been waived or deferred**.** They often provided no rationale for a waiver or deferral and no information about the kind of deferred study that would be expected. In some cases, the decision about deferral or waiver was itself deferred. Recent letters are generally specific about the applicability of PREA requirements and the rationale for determinations.

In an analysis required by Congress in 2007, FDA's PeRC analyzed the extent to which FDA approval letters or other documents were citing appropriate rationales for waiving or deferring pediatric studies under PREA (PeRC, 2010). The retrospective

[6] For example, in June 2011, FDA approved a tamper-proof tablet form of an opioid product (oxycodone HCl [Oxecta]) for which no studies were required under PREA because it considered this not to be a new form (Rappaport, 2011b). It has considered extended-release tablets, among other types of tablets, to be a new dosing form (see Appendix C in FDA's Orange Book [FDA, 2011b]).

review of actions taken between January 1, 2004, and September 27, 2007, found that 22 percent of the waivers were granted for reasons other than those specified in PREA of 2003 and another 10 percent incorrectly applied the specified criteria. Examples of incorrect rationales included explanations that no appropriate formulation was available. (PREA allows FDA to direct a sponsor to try to develop such a formulation if necessary for pediatric studies.)

The most common basis for waivers was that studies would be impossible or highly impracticable. Other waivers were based on safety concerns. In the PeRC sample, no waivers were based on the rationale that the product did not represent a meaningful therapeutic benefit over existing therapies and would not be expected to be used by a substantial number of pediatric patients. The committee identified some examples of such waivers, for example, for studies of benzyl alcohol (Ulesfia) to treat head lice in children ages 1 to 6 years (Beitz, 2009b).

In contrast to the pattern for waivers, nearly all (98 percent) of the rationales for deferrals were consistent with the law. The most common reason for deferral was that a product was ready for approval for adults.

In addition to the findings about waivers and deferrals, PeRC identified problems with scientific quality, particularly in the early years following the enactment of PREA in 2003. Consistent with the shortcomings described above for written requests, these included inadequate processes for selection of the study dose and inadequate numbers of subjects for realistic statistical assessment, both of which are problems that could have contributed to the failure of studies to find efficacy. The report concluded that a more detailed pediatric plan or more specific recommendations from the review division might have avoided the problems.

Specifications for Types of Studies Required

As noted above, some approval letters, particularly early letters, did not mention PREA requirements, whereas others noted a requirement for deferred studies but provided no specifics beyond those for the age group involved. The most recent letters tend to be considerably more detailed than earlier letters in specifying the kinds of studies required, although they are less detailed than a written request.

The 2011 letter approving an NDA for albumin (human) (Kedbumin) provides an example of a more detailed specification. It described a requirement for a "prospective, randomized, multicenter, controlled open label study to evaluate the safety of Kedbumin 25% compared to normal saline solution in the treatment of post-surgical hypovolemia associated with hypoalbuminemia in pediatric patients undergoing major elective surgery" that would "enroll a total of 100 subjects, 50 subjects in each treatment cohort, with approximately equal numbers of subjects in the following subpopulations": 1 day up to 2 years, 2 up to 6 years, and 6 up to 12 years (Malarkey and Epstein, 2011, unpaged). Other recent letters specify more than one required study. In one example involving a product for topical treatment of plaque psoriasis, the agency specified pharmacokinetic/dynamic studies for children ages 2 through 11 years and ages 12 through 16 years and also specified a safety and efficacy study for the younger age group (Walker, 2010).

Sponsor plans for the study of products for pediatric use are not made public, so the committee could not assess the plans submitted for products included in its sample. In conversations, FDA staff described the pediatric research plans submitted by sponsors as variable, ranging from well thought out to perfunctory. In the one example that the committee found online (BPL, 2009), the pediatric research plan was approximately as detailed as many of the written requests that the committee reviewed. It included a proposed clinical study approach with a description of the proposed design, the age groups to be studied and number in each group to be studied, the entry criteria, the primary and secondary efficacy endpoints, the safety variables, the timing of various assessments, and the general types of statistical analyses to be provided.

Status of Deferred Studies

The timely initiation, completion, and reporting of studies required under PREA are important to meeting the objectives of the law. Likewise, FDA's timely assessment of NDAs or BLAs submitting studies required under PREA is important. Responding to concerns that postmarket studies required by FDA were not being adequately monitored or completed in a timely fashion (or at all), Congress in 1997 required that FDA monitor and make public information on the status of studies that have been agreed to by sponsors (21 USC 356b).

Beginning in 2007, Congress also required studies undertaken in response to a PREA requirement to be submitted in a supplemental NDA or BLA that required approval (see Chapter 3). Prior to that provision, sponsors might submit reports in general correspondence or other forms that did not trigger explicit FDA response and labeling determinations, thereby undermining a key objective of the law.

FDA established a website that allows individuals to inquire about postmarket study requirements or commitments, including those required under PREA.[7] FDA also posts summary reports on studies deferred, waived, and completed under PREA. Table 7-1 presents information on the status of deferred studies in the years from September 2007 through 2010.[8]

In 2010, FDA counted 63 (15 percent) deferred studies as delayed; 262 (63 percent) as pending but not defined as delayed; and 36 as ongoing. In the same year, 24 deferred studies were submitted to FDA; another 14 were judged by FDA to fulfill requirements; and sponsors were released from requirements for 12 studies. From 2008 to 2010, the number of pending studies grew by almost 50 percent while the number of delayed studies increased by more than 80 percent. Without information that is not public, it is hard to evaluate these numbers.

[7] The site does not generate an easily used comprehensive listing of those requirements. The descriptions of the studies vary in specificity (e.g., identification of age groups). As the committee conducted its assessment of studies conducted under PREA, it discovered some products that should have been but were not included in the database and notified FDA so the agency could add the information.

[8] For these and earlier years, FDA has also published in the *Federal Register* annual status reports for several types of required postmarket studies. Before 2008, these reports did not break out information on studies required under PREA.

TABLE 7-1 Progress of Pediatric Studies Deferred Under PREA, 2007 to 2010

	No. (%) of Studies			
Study Status	9/27/2007	2008	2009	2010
Pending	188 (83)	180 (60)	219 (60)	262 (63)
Ongoing	8 (4)	26 (9)	32 (9)	36 (9)
Submitted	16 (7)	26 (9)	33 (9)	24 (6)
Fulfilled	2 (1)	17 (6)	14 (4)	14 (3)
Released	1 (<1)	12 (4)	18 (5)	12 (3)
Delayed	11 (5)	35 (12)	46 (13)	63 (15)
Terminated	1 (1)	3 (1)	3 (1)	3 (1)
Total Studies	227 (100)	299 (100)	365 (100)	414 (100)
Total Products	190	230	263	267

NOTES: Pending indicates that the study has not been started but it is not considered delayed. Ongoing indicates that the study is on or is ahead of the original schedule. Submitted indicates that the applicant has concluded or terminated the study and has submitted a final report but that FDA has not notified the applicant in writing that its study commitment has been fulfilled or released. Fulfilled indicates that the applicant has submitted the final study report and that FDA has determined that the applicant has met its study commitment. Released indicates that FDA has released the applicant from its obligation because the study is either no longer feasible or no longer useful. Delayed indicates that the study is behind the original study schedule. Terminated indicates that the applicant ended the study before completion but has not yet submitted a final study report.
SOURCE: Compiled from information at http://www.fda.gov/downloads/ScienceResearch/SpecialTopics/PediatricTherapeuticsResearch/UCM195000.pdf.

An FDA-commissioned analysis of the backlog of postmarket studies (not limited to those required under PREA) provides some perspective. It found that PREA studies accounted for a somewhat larger share of delayed studies than of total studies in the backlog (Booz Allen Hamilton, 2010). Of the 220 PREA studies in the backlog, 6 had been issued without a specified completion date. An earlier analysis that excluded PREA studies found that difficulty with patient enrollment was the most common reason that a study had been categorized as delayed (Booz Allen Hamilton, 2008). Such difficulties are also likely to be a factor in delayed PREA studies as well as in the release of sponsors from requirements for studies.

The committee did not locate a report that charted the status of PREA requirements by year, for example, how many studies that were originally specified in 2004 were pending, fulfilled, or otherwise categorized as of the end of 2010. Chapter 3 explained that FDA has limited leverage to compel completion and submission of a required study and suggested that Congress provide the agency with more flexibility to impose sanctions, including monetary penalties, for unreasonably delayed pediatric studies.

PEDIATRIC DRUG STUDIES AND FDA REVIEWS

As explained in Chapter 5, the committee did not have direct access to the voluminous submissions by study sponsors of study findings and other information (and would not, in any case, have had the resources to review them). Rather, the committee relied on the reviews of FDA staff, generally including the clinical review, the clinical pharmacology review (if any), and the statistical review (if any). In some cases, for example, when there was disagreement about conclusions, the initial clinical review was supplemented by memoranda from the review team leader or division director (or both) commenting on some aspect of the review. Some reviews cited discussions by FDA advisory committees, and summaries of those discussions were consulted if available.

In several reviews that the committee examined, the redaction of significant sections created problems for the committee's analyses, especially when the redactions covered the reviewer's overall conclusions and recommendations (see Chapter 5). In conversations, FDA staff explained that the criteria for redaction were related not only to confidential or proprietary information but also to issues involving negotiation with sponsors (e.g., about labeling language) or agency deliberations (e.g., reviewer judgments that were not upheld as they went through levels of organizational review). Chapter 4 of this report suggests that Congress ask for an independent assessment of the extent to which such redactions are appropriate.

Quality of FDA Reviews

For the most part, the committee judged the FDA reviews, especially the more recent reviews, to be of good quality. As described in Chapter 5, recent reviews that follow the Center for Drug Evaluation and Research template help the reader identify important information and conclusions about safety and efficacy. CBER had not formally adopted such a template. Heavily redacted reviews were of limited use, but that issue was not under the control of the reviewers.

Some reviews included little discussion of developmental variability when the committee judged such discussion to be warranted, for example, for findings (or absence of findings) for neonates or adolescents. The committee did not attempt to identify whether reviewers had pediatric training or experience.

Chapter 5 also notes that clinical reviewers typically did not say much, if anything, about the appropriateness or validation of alternative endpoints used in efficacy studies and that it would be desirable for such discussion to be added to reviews (and written requests). Likewise, the justification for the use of extrapolation could be expanded, although the law requires only brief documentation.

The PeRC report cited above commented that review of FDA assessments of sponsor submissions varied across divisions, including the level of detail used in reviewing protocols for pediatric studies. The reviews in this case were not reviews of pediatric studies required under PREA but the prior reviews that included the evaluation of sponsor plans for pediatric studies. The committee did not attempt to assess variability across divisions but expects that variability across divisions likewise exists for clinical reviews. A recent IOM report (2010) noted variability in FDA evaluations of studies

submitted under the Orphan Drug Act and recommended that the agency investigate the extent to which such variability is appropriate.

Types of Studies Supporting Labeling Changes

In 2007, Congress required FDA to begin reporting certain characteristics of studies conducted under BPCA and PREA, including the types of studies submitted by sponsors to support labeling changes or pediatric exclusivity determinations. Of the requested or required studies reported since then, FDA has classified two-thirds (229 of 346) as efficacy and safety studies (Table 7-2). Studies are labeled by their primary purpose, although pharmacokinetic studies typically yield some information about a drug's safety. Similarly, some findings relevant to efficacy may be reported in these studies and in safety studies.

TABLE 7-2 Types of Pediatric Studies for Labeling Changes Conducted Under BPCA and PREA Between September 27, 2007, and June 30, 2011

	No. (%) of Studies			
Type of Study	BPCA	BPCA + PREA	PREA	Total
Efficacy/safety	36 (61)	28 (41)	165 (75)	229 (66)
PK/safety	10 (17)	30 (44)	17 (8)	57 (16)
PK/PD	5 (8)	7 (10)	3 (1)	15 (4)
Safety	8 (14)	3 (4)	23 (10)	34 (10)
Other	0 (0)	0 (0)	11 (5)	11 (3)
Total	59	68	219	346

NOTE: These studies were associated with 130 different products, 13 of which were vaccines (personal communication, Catherine Lee, Office of Pediatric Therapeutics, FDA, July 26, 2011). The table does not necessarily include Phase I or Phase II studies and thus likely undercounts pharmacokinetic studies. Also some pharmacokinetic studies may be incorporated in efficacy/safety studies (personal communication, Catherine Lee, Office of Pediatric Therapeutics, FDA, October 5, 2011). PK = pharmacokinetic; PD = pharmacodynamic.
SOURCE: This information is periodically updated and is available online at http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm190622.htm.

More than 70 percent of all studies (219 of 346) for the time period covered were associated solely with PREA requirements; another 12 percent (68 of 346) were associated with both BPCA requests and PREA requirements, and 17 percent were linked to BPCA requests. About 75 percent of studies that were conducted only under PREA requirements were for both efficacy and safety as were about 60 percent of the studies associated solely with BPCA requests. For reasons that are not obvious, the studies that were related to both BPCA requests and PREA requirements were more likely to involve safety and pharmacokinetics rather than safety and efficacy.

Issues in Pediatric Studies Submitted for FDA Review

Many studies that the committee reviewed generated valuable information, including, in some cases, negative information about unexpected adverse events or lack of efficacy. Examples of informative labeling changes resulting from these studies are discussed in the next section.

This section focuses on studies that did not reach their potential. To the extent that original or amended written requests failed to specify appropriate trial design and associated measures and methods, the resulting studies may have corresponding weaknesses. For example, if the written request has shortcomings in the specification of endpoints, dose-finding strategy, study design, or sample adequacy (including pediatric subgroups), then the studies as conducted and submitted to FDA are likely to suffer unless appropriate amendments to the request change the terms.

Similar problems may arise with studies conducted under PREA if the protocol review process for studies is limited or lacking in appropriate pediatric expertise. As observed in the PeRC report cited earlier "[w]here there was evidence of specific discussion and documentation of the studies needed to fulfill the PREA requirements before commencement and/or submission of the studies, the PREA assessments [i.e., the studies conducted by the sponsor] generally were of higher quality" (PeRC, 2010, p. 10).

In a few cases, however, problems appeared to arise as much or more from the execution of requested or required studies as from the specifications for the studies. Box 7-3 provides examples of aspects of study planning or execution that may have limited the usefulness of the information submitted. (Chapter 6 discussed problems with written requests and studies that stem from uncertainties about the nature of GERD and bacterial conjunctivitis in neonates.)

BOX 7-3
Aspects of Studies as Planned or Executed That May Have Limited the Usefulness of Information Submitted

Questions about participant characteristics and dosing issues. For the pivotal study of omalizumab (Xolair) for the treatment of moderate to severe persistent asthma in children ages 6 to 11 years (inclusive), the children enrolled in studies had, on average, normal pulmonary function (determined from the forced expiratory volume in 1 second [FEV1]). As summarized by the clinical reviewer, an FDA advisory committee was concerned that "the applicants had not studied patients for whom the drug is intended, namely the most severe asthmatic patients who are not responding to alternative therapies" and was "very concerned that the applicants had not explored any dose ranging" for this age group (Starke, 2009, p. 95). Taking the results for all efficacy endpoints and safety data into account, the advisory committee concluded that the risk-benefit assessment did not favor approval of the product. Almost all of the overview of the risk-benefit section of the review was redacted.

Questions about adequacy of dosing. In requested studies of leflunomide (Arava), children with juvenile rheumatoid arthritis receiving this drug showed less improvement than children in the active comparator (methotrexate) control arm of the trial (68 versus 89 percent) (Yancey, 2003). On the basis of questions about the adequacy of the dosing used for lower-weight children, the

drug was labeled in 2004 as having not been fully evaluated. The label included information about pharmacokinetics and safety and a summary of the trial results.

Problems with data quality. In analyzing a submission of studies of zolmitriptan (Zomig) for treatment of migraine in adolescents, the statistical reviewer described "extreme difficulties in analyzing the data due to poor data quality, missing information (information not entered in the data by the sponsor), poor organization of the data, and various errors" (Yan, 2008, p. 4). The reviewer also noted problems with poor patient compliance and with the deviations from the statistical analysis plan in the sponsor's imputation of efficacy values. The reviewer concluded that no statistically significant difference existed between the test drug and the placebo for either 1-hour headache response or 2-hour sustained headache response.

Inadequate enrollment of relevant age groups. One of two studies described in the written request for propofol (Diprivan), which anesthesiologists use in all age groups, was a randomized, open-label trial comparing 1 percent propofol versus standard anesthetic technique for induction and maintenance of general anesthesia in children from birth to 3 years of age (Raczkowski, 1999). The request specified "substantial representation" of three age groups, including children from birth to 2 months of age. In reviewing the study as conducted, the clinical reviewer concluded that "the only age group not adequately covered was the birth to <2 month age group" (Hartwell, 2000, p. 66); only one neonate was in the propofol arm, whereas four were in the standard anesthetic arm. The labeling states that the product is not recommended for maintenance of anesthesia in this age group because safety and effectiveness have not been established.

Safety concern not addressed. In a study of sotalol (Betapace) for treatment of arrythmias, the reviewer noted higher peak concentrations of the drug in neonates and infants than older children and attributed some of the difference to differences in renal function (Karkowsky, 2000). The studies enrolled fewer neonates than planned (6 rather than 20). In general, the reviewer notes that the studies provided no information about dosing of children who have diminished renal function.

Questions about pediatric subgroup. Guanfacine hydrochloride (Intuniv) was studied for treatment of attention deficit-hyperactivity disorder in children ages 6 to 17 years of age. For the 13- to 17-year-old age group, the studies did not find a statistically significant different result for the study drug than for the placebo. The clinical reviewer noted that the sponsor used fixed rather than flexible, weight-based doses in the trials and concluded that "it is highly likely that one contributing factor [to the study results] was the lower serum guanfacine exposures observed in the Intuniv clinical program" (Levin, 2007, p. 43) The product was approved for the entire age group with a weight-based dosing regimen, labeling that described the study results, and a postmarket commitment for an additional study with adolescents to confirm efficacy.

Weak trial design. Etodolac (Lodine XL) was studied for treatment of juvenile rheumatoid arthritis in children 6 to 12 and 12 to 16 years of age in an open-label uncontrolled trial to assess pharmacokinetics, safety, and efficacy. The clinical reviewer concluded that "especially without some arm for comparison, it is difficult to understand how any of this information can be placed into a proper context short of historical controls either in an adult or pediatric population" (Witter, 1999, p. 17). The pharmacometrics reviewer concluded "that no statistical comparison can be made on pediatric and adult PK [pharmacokinetics] based on the studies submitted" (Wang, 2000, p. 14). The pediatric section of the label approved in 2000 read, "If a decision is made to use Lodine XL for patients six years of age or older, as with other NSAIDs [nonsteroidal anti-inflammatory drugs], such patients should be monitored periodically" (http://www.accessdata.fda.gov/drugsatfda_docs/nda/2000/20-584S005_Lodine_prntlbl.pdf). By

2005, however, the label had been amended to add that safety and effectiveness in patients 6 to 16 years of age were supported by extrapolation from adult trials and by safety, pharmacokinetic, and efficacy data from an open-label trial with children in that age group (http://www.accessdata.fda.gov/drugsatfda_docs/label/2005/020584s004,006,007lbl.pdf). It is not clear what prompted that change, which is not recorded in FDA's overview table of BPCA- and PREA-related labeling changes.

Problems with administration of test and control drugs. In a trial of fluticasone inhalation aerosol (Flovent) investigated in children 6 to 23 and 24 to 47 months of age, the report for the pharmacokinetic study revealed detectable levels of the study drug in some participants in the placebo control arm. Further investigation also showed that some participants in the test arm had no detectable levels of the test drug. The reviewer concluded that "the studies could not be meaningfully interpreted, and no conclusions may be drawn regarding either efficacy or safety from the clinical studies" (Starke, 2003, p. 5).

In one instance, the committee found unusual labeling language that conveyed FDA's dissatisfaction with the sponsor's design and conduct of a study of a drug to reduce mortality and morbidity in neonates and infants with cyanotic congenital heart disease palliated with a systemic artery-to-pulmonary artery shunt. The reviewer particularly cited deficiencies in the sponsor's approach to selecting the dose for study, which the reviewer and others at FDA concluded was too low to have the desired antiplatelet effect (Rose, 2010; Grant, 2011). Other problems included the concomitant use of aspirin and the late initiation of therapy. After noting the study results and these likely contributing factors, the label goes on to state that "[i]t cannot be ruled out that a trial with a different design would demonstrate a clinical benefit in this patient population" (BMS/SPP, 2011).

In addition to problems with various aspects of study design, studies may not be completed to the standard desired—or at all—because sponsors encounter difficulties with enrollment of sufficient numbers of children, despite reasonable efforts. This challenge of pediatric studies was highlighted in Chapter 1. In the committee's sample, one example of such enrollment problems involved a study comparing leflunomide (Arava) to methotrexate for treatment of juvenile rheumatoid arthritis. Enrollment shortfalls prompted the amendment of the written request to specify a superiority trial with 94 participants instead of the originally requested noninferiority or equivalence trial with 120 participants (Yancey, 2004). The efficacy findings for the randomized, double-blind trial favored the active comparator.

Another example of enrollment difficulties involved a combined pharmacokinetic, safety, and efficacy trial testing pegfilgrastim (Neulasta) to reduce episodes of febrile neutropenia in children with sarcoma. Of 50 eligible study sites, only 18 agreed to participate in the trial; of these, only 10 enrolled any children (Summers, 2008). A likely contributing factor was that pefilgrastim was already marketed and available, so parents may have been reluctant to have their child participate in a trial comparing the drug, which involved a single injection, to neupogen, which required daily injections. Some pharmacokinetic information was added to the labeling. FDA judged the sponsor to have made diligent effort to fulfill PREA requirements and noted that the Children's Oncology Group (COG; which is centrally involved in the conduct of most pediatric cancer trials in the United States) had indicated to the sponsor that the conduct of an additional efficacy

study of the drug was not a priority. For another pediatric cancer drug study, which was ended early for lack of evidence of test drug activity, a different reviewer noted that because relatively few children are diagnosed with cancer compared with the number of adults, "COG prioritizes its trials to study the most promising agents first" (Honig, 2002, unpaged).

PEDIATRIC STUDIES AND CHANGES IN LABELING

Types of Labeling Changes

All but one of the products in the committee's sample had labeling changes that resulted from the studies conducted under BPCA or PREA. Three labeling changes involved one product. Of the 45 labeling changes in the sample, 17 involved the extension of age limits for an indication that had already been approved in adults or another pediatric age group. Another 10 changes involved approval of a new product with pediatric labeling or a new indication that had not previously been approved for adults. Thus, 60 percent of labeling changes in the sample resulted from studies that found efficacy and safety. (In a few cases, changes involved studies for which efficacy studies were not required.) The addition of an indication to labeling was generally accompanied by information on dosing, pharmacokinetics, and safety. As described in Chapter 6, five products studied with substantial numbers of neonates did not have a labeling change that incorporated any information from these studies.

For the labeling changes that did not involve the addition or expansion of a pediatric indication, changes generally included the addition of some information about safety and pharmacokinetics. For changes that followed from studies that did not show efficacy, the presentation of that information varied. Some labels added statements to the effect that use of the product was not indicated or recommended, whereas others stated that safety and efficacy had not been established for all or some pediatric age groups. The latter language is rather imprecise, in itself not making clear whether studies have not been conducted and submitted to FDA or whether studies have been submitted and did not show safety and efficacy. Additional text in the label may clarify the situation, but the key summary sentence is still ambiguous, especially as it appears in the first page of a labeling summary.

FDA has not evaluated information added to the label as a result of studies required under PREA, but FDA staff have published two articles that have reviewed labeling changes associated with BPCA (Roberts et al., 2003; Rodriguez et al., 2008). The most recent article presents data from an analysis of labeling changes from July 1998 through October 2005 (Rodriguez et al., 2008). For the108 drugs with labeling changes resulting from to studies conducted under BPCA, 77 changes extended the age limits for an approved indication; 19 changes added information about lack of efficacy. Of the other changes, 23 involved dosing or pharmacokinetic information, 34 involved safety, and 12 described a new pediatric formulation. The discussion and examples focused on the changes related to new information on pharmacokinetics or dosing.

The analysis by Rodriguez and colleagues (2008) stressed the importance of studies requested under BPCA to generate knowledge important for safe and effective

dosing. It noted that the results of studies were not necessarily predictable on the basis of weight differences and data from adults.

For the sample that the committee examined, Box 7-4 presents examples of informative changes to labeling resulting from requested or required pediatric studies. Most changes supported the use of the drug with children but some did not. Some changes reflected safety findings for children that differed from findings for adults.

BOX 7-4
Informative Labeling Changes

Vinorelbine tartrate injection (Navelbine) (2002). Requested studies did not show activity of the drug against recurrent malignant solid tumors, which is important information for clinicians. Labeling noted that toxicities were similar to those in adults. Recent studies suggest that the drug may have value against other cancers; the clinical review is not publicly posted by FDA but includes pharmacokinetic data that could be useful to investigators.

Remifentanil (Ultiva) (2004). Requested studies with infants from birth to 2 months of age showed high variability in the drug's phamacokinetics in neonates, which led FDA to recommend careful titration of individual doses. Given concerns about possible negative neurodevelopmental effects of anesthetics in young children, the information about an ultra-short-acting opioid without suspected neurotoxic effects is valuable.

Desflurane (Suprane) (2006). Requested studies clarified the risks from use of this anesthetic, which is approved for maintenance of anesthesia in pediatric patients with intubation and after induction with another agent. The studies led to stronger safety information in the labeling stating that the product is not approved for maintenance of anesthesia in nonintubated children. The warning now appears at the front of the labeling, a change made possible by the switch in 2010 to the structured labeling format that FDA has been phasing in since 2006.

Aripiprazole (Abilify) (2007, 2008). This drug has a different mechanism of action than other antipsychotic medications available at the time that written requests were issued. Studies led to labeling for pediatric use for the treatment of schizophrenia and mania associated with bipolar disorder. Under PREA, the drug has also been approved for treatment of irritability associated with autism.

Adalimumab (Humira) (2008). Required studies of children with juvenile idiopathic arthritis demonstrated efficacy. They also found several safety signals that had not been identified in adults, including elevations of creatine phosphokinase, a higher rate of immunogenicity, and a higher rate of nonserious hypersensitivity reactions.

Tenofovir disoproxil fumarate (Viread) (2010). Several factors complicated the required study of this drug's efficacy for treatment of HIV infection in adolescents, but the pharmacokinetic and safety data combined with adult data allowed the extrapolation of efficacy to this pediatric age group. Although the drug has been used in adolescents on the basis of a favorable toxicity profile in adults and pharmacokinetics that allow once-a-day dosing, the studies provided reassurance for such use on the basis of the safety and pharmacokinetic results. (Based on these studies and studies with adults suggesting adverse bone effects, FDA required a postmarket clinical trial to further investigate the drug's effects on bone in pediatric patients.)

Candesartan (Atacand) (2009). Requested studies of children ages 1 to 17 years showed safety and efficacy of the drug for the treatment of hypertension. The pharmacokinetic data provided the basis for dosing recommendations for children ages 1 up to 6 years and children ages 6 up to 17 years. Other data for children less than 1 year of age led FDA to drop the requested study with children less than 1 year of age and to specifically warn in the label that the product must not be used by this age group.

As discussed in Chapter 5, FDA sometimes requests only pharmacokinetic and safety information and expects to extrapolate efficacy on the basis of efficacy studies with adults, absent unexpected safety findings. In the case of sotalol (Betapace), FDA requested pharmacokinetic, pharmacodynamic, and safety information to guide pediatric use but did not request efficacy studies and did not extrapolate safety and efficacy from adults. The labeling for the product notes that safety and efficacy have not been established, but it includes pediatric dosing and pharmacokinetic information (for children more than 2 years of age and children younger than that) based on two requested studies (FDA, 2001).

Box 7-5 presents examples of committee concerns about the labeling changes that followed pediatric studies. Most involve how labels presented information about pediatric studies that did not demonstrate efficacy.

BOX 7-5
Concerns about Clarity of Labeling Changes

Information appears to be contradictory. The labeling for zoledronic acid (Zometa) states that it is not indicated for use in children but also states (as in the previous label) that "[b]ecause of long-term retention in bone, Zometa should only be used in children if the potential benefit outweighs the potential risk" (NPC, 2011, unpaged). That advice applies to the use of any medication by children or adults.

Lack of efficacy is downplayed. The pediatric use section of the labeling for buspirone (Buspar) does not state that efficacy has not been demonstrated. Rather, it describes safety and pharmacokinetic data from two placebo-controlled trials and that the trials found "no significant differences between buspirone and placebo with regard to the symptoms of GAD [generalized anxiety disorder] following doses recommended for the treatment of GAD in adults" (BMS, 2010, p. 11).

Lack of efficacy in an age group not explicitly stated. The pediatric use section of the labeling for olmesartan (Benicar) notes that it was studied in children ages 1 to 16 years and that it was generally well tolerated and had an adverse experience profile similar to that for adults. It does not explicitly state that studies did not show efficacy in the younger age cohort studied (ages 1 to 5 years).

Lack of advantage of higher dose could have been clearer. In the "front-page" highlights of prescribing information for aripiprazole (Abilify) for treatment of schizophrenia in adolescents, the dosing chart lists a maximum dose without noting that it was not shown to be more effective than the recommended dose. The discussion of dosing later in the labeling notes this. The

discussion of adverse events does not discuss the effects of the higher dose on adverse events (e.g., somnolence and extrapyramidal effects).

Relevant data about dosing were not highlighted. Studies of mometasone furoate **(**Asmanex) yielded convincing data that twice-a-day administration of the 110-mg dose to children ages 4 to 11 years was more efficacious than once-a-day dosing for severe asthma. This data does not have a prominent place on the label.

Placement of information is unexpected. Data on the pharmacokinetics of irinotecan hydrochloride (Camptosar) are included in the precautions section of the labeling rather than in the section on clinical pharmacology. The latter section does not provide a cross-reference to the precautions section, which begins by explaining that studies had not demonstrated effectiveness for the treatment of solid tumors in pediatric patients.

In some cases, labeling seemed to convey contradictory information, as illustrated in the first example in Box 7-5. Such labeling may stem from the dilemma faced by FDA in labeling of products that it expects may have continued off-label use, despite studies that do not demonstrate efficacy. It may also stem from FDA concerns about the shortcomings of efficacy studies (e.g., enrollment problems) that might have limited the possibility of finding statistically significant positive findings for a drug that is, in fact, efficacious.

Aside from specific language in labeling, another concern stems from the incomplete transition from the old labeling format to a new format, which was introduced in 2006, as described in Chapter 3. Of the 45 labeling changes in the committee's sample, the labeling for 15 products remained in the old labeling format at the time that it was consulted. That is, FDA has not required the sponsor to revise the label to meet current standards for new labeling that, in particular, requires a front page that summarizes key information about approved uses and age groups (ideally), warnings, and use by special populations.

Reformatting can significantly clarify information. For example, when the labeling for desflurane (Suprane) was reformatted, the front-page segment on pediatric use highlighted that for safety reasons the product was not recommended for induction of anesthesia in or for maintenance of anesthesia in nonintubated children. In the old format, the indications and usage section did not explicitly state that it was not recommended for the latter use.

Although the committee was not asked to evaluate the efforts by FDA or others to disseminate information from pediatric studies and labeling changes, it recognizes that these efforts are important. The committee is aware that clinicians often do not consult a product's labeling. They instead rely on intermediary sources, as described in Appendix B. Nonetheless, to the extent that old labels are consulted by clinicians or others, including parents searching the Internet for additional information on a child's treatment, the format hinders the identification of key information about efficacy and safety. To acknowledge the importance of getting information to clinicians, the committee commissioned the background paper that appears in Appendix B. It underscores the challenges of getting up-to-date information to clinicians who care for children.

CONCLUSIONS

Pediatric studies conducted under BPCA and PREA are yielding important information to guide clinical care for children. The information generated varies by medical condition and age group. As discussed in Chapter 6, studies with neonates are a particular challenge. Findings from pediatric studies sometimes support and sometimes run counter to expectations about the efficacy, safety, and pharmacokinetics of a drug in children of different ages.

Some studies requested under BPCA or required under PREA do not achieve their full potential. Reasons vary. Some problems stem from the use of weak study designs and underpowered samples, the lack of dose-ranging studies to guide efficacy trials, and the omission of relevant information from labels. Other problems stem from sponsor difficulties enrolling sufficient numbers of children in clinical trials. *One persistent need is for strict and consistent attention by FDA, sponsors, and investigators to dose selection for evaluation in pediatric drug studies.*

The committee concluded that the steps that Congress and FDA have initiated appear to be improving the quality of requests and requirements for pediatric studies. These steps include increased review by pediatric experts, increased specificity in the template for written requests and amendments to specific written requests, and earlier specificity about deferred studies required under PREA. In addition, as suggested in Chapter 4, *FDA could more clearly articulate the health benefits expected of requested studies so that children do not participate in research of minimal value.* Chapter 5 suggested similar articulation of the rationales for the acceptance of extrapolation and the use of alternative endpoints.

Although FDA now monitors, analyzes, and reports more information about the status of studies (e.g., required studies that are pending or delayed and clinical areas represented by written requests), some information is not readily available. If FDA creates a formal system for tracking pediatric drug applications through the submission and review process as recommended by GAO, it would be helpful for the system to track pediatric studies by age group, including neonates specifically.

The organization and highlighting of key information in the current structured labeling format are substantial improvements over the previous version. *Transitions to the new format provide FDA with the opportunity to clarify inadequately described, ambiguous, or contradictory information in older labeling.*

The committee recognizes that FDA faces some dilemmas when submitted studies do not show efficacy but the agency expects that physicians will continue to use the drug off-label. If the agency includes pharmacokinetic and safety data in labeling, it is important that the label be clear that the provision of information about pediatric dosing does not mean that the product is recommended for pediatric use. FDA likewise faces dilemmas when off-label use of a medication is common but controlled studies of efficacy are not or may not be feasible. The agency may have to weigh competing risks. If it requests or requires sponsors to conduct only pharmacokinetic and other studies to guide dosing decisions, it risks encouraging increased use of a product that has not been demonstrated to be effective. If it does not seek this information in the absence of more

comprehensive investigations, it leaves physicians without data that could potentially reduce the harm or increase the benefit from off-label use.

In the future, FDA's efforts to strengthen regulatory science (e.g., methods for evaluating drugs and biologics) should support further improvements as should a number of activities the agency has undertaken to analyze specific challenges in pediatric trial design and analysis and propose innovative strategies to meet these challenges. Examples include the analyses of pediatric hypertension trials described in this chapter and the assessment of pediatric studies of analgesic medication and other pain prevention and alleviation strategies described in Chapter 6. *To improve pediatric studies of drugs and biologics and their evaluation, it is important for FDA to continue and expand initiatives to strengthen the science base for its work, analyze shortcomings in pediatric studies, and develop innovative strategies to meet the specific challenges of pediatric trials.*

8
Pediatric Studies of Biologics

Until recently, the incentives of the Best Pharmaceuticals for Children Act (BPCA) were not available to sponsors of products defined as biologics. These products have, however, been subject to the requirements for pediatric studies of the Pediatric Research Equity Act (PREA) and its predecessor, the Pediatric Rule. The Biologics Price Competition and Innovation Act (BPCIA), which was included in the Patient Protection and Affordable Care Act of 2010 (PL 111-148), substantially reshaped the regulation of biologics. As described below, it made products regulated under the Public Health Service (PHS) Act eligible for the incentive of pediatric exclusivity.

BPCIA also replaced certain provisions for this Institute of Medicine (IOM) study that had been included in the Food and Drug Administration Amendments Act of 2007 (FDAAA).[1] One of the new provisions called for the IOM to "review and assess the number and importance of biological products for children that are being tested as a result of the amendments made by the Biologics Price Competition and Innovation Act of 2009 and the importance for children, health care providers, parents, and others of labeling changes made as a result of such testing." A second provision called for the review and assessment of "the number, importance, and prioritization of any biological products that are not being tested for pediatric use." Under the third new provision, the IOM was to "offer recommendations for ensuring pediatric testing of biological products, including consideration of any incentives, such as those provided under this section or section 351(m) of the Public Health Service Act."[2]

This chapter outlines the incentives for pediatric studies included in BPCIA and explains why it is too early to assess the impact of these incentives or offer recommendations. It also summarizes information about biological products that have been studied, are being studied, or are pending study with children and then identifies a small number of products that appear not to have been the subject of pediatric studies. As context for this chapter, Appendix C describes some differences between small-molecule drugs and biologics and also reviews information about the use of biologics by children. Appendix D includes tables listing 97 biological products with summary information

[1] The 2007 provisions had called for the IOM to review and assess pediatric studies of biological products required under PREA and to make recommendations about incentives to encourage pediatric studies of biologics.

[2] Section 351(m) covers incentives for pediatric studies of biologics added to the PHS Act by BPCIA.

about pediatric studies identified in product labeling or in a public database of clinical trials.

ENSURING PEDIATRIC STUDIES OF BIOLOGICS

Biologics Price Competition and Innovation Act

The primary objective of BPCIA was to create a pathway to licensure for biological products that are demonstrated to be biologically similar (biosimilar) to and, in some cases, interchangeable with a previously licensed biologic.[3] In 1984, when Congress created a pathway for the approval of less expensive generic versions of drugs regulated under the Food, Drug, and Cosmetic (FDC) Act, no analogous pathway was created for products regulated under the PHS Act. At the time, modern biotechnology was in its early days, so the lack of such a pathway was not a particularly pressing issue.

Congress has defined the terms *biosimilar* and *interchangeable*. As summarized by FDA in 2010,

> A biological product may be demonstrated to be "biosimilar" if data show that the product is "highly similar" to the reference product notwithstanding minor differences in clinically inactive components and there are no clinically meaningful differences between the biological product and the reference product in terms of safety, purity and potency. (75 FR 61497)
>
> To meet the higher standard of "interchangeability," a product must demonstrate that it can be expected to produce the same clinical result as the reference product in any given patient and, if the biological product is administered more than once to an individual, the risk in terms of safety or diminished efficacy of alternating or switching between the use of the biological product and the reference product is not greater than the risk of using the reference product without such alternation or switch. Interchangeable products may be substituted for the reference product by a pharmacist without the intervention of the prescribing health care provider. (75 FR 61497 at 61498)

BPCIA provides for a 12-year period of exclusivity for an innovative (reference) biological product following its approval. During that period, the Food and Drug Administration (FDA) cannot approve a biosimilar product. In addition, the sponsor of an application for a biosimilar product cannot submit its Biologics License Application

[3] As described in Chapter 3, for regulatory purposes, a *biologic* is "a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, protein (except any chemically synthesized polypeptide), or analogous product, or arsphenamine or derivative of arsphenamine (or any other trivalent organic arsenic compound) applicable to the prevention, treatment, or cure of a disease or condition of human beings" (42 USC 262(i)). A few older products that were originally derived from human or other animal sources (e.g., insulin, human growth hormone, and certain enzymes) are regulated under the FDC Act rather than the PHS Act and were covered by BPCA from the outset.

(BLA) to FDA until 4 years after the date on which the reference product was first licensed.

By creating the new periods of exclusivity for biologics, this law provided the basis for the key incentive of BPCA: the 6-month extension of exclusivity for sponsors that conduct pediatric studies of a product in response to a written request from the FDA. Thus, to the 12-year and 4-year periods of exclusivity created by the 2010 law, a grant of pediatric exclusivity for the completion of requested studies would provide 6 further months of marketing protection. In addition, the 2010 law included explicit provisions for the application of the BPCA incentive to both new and previously marketed biologics (42 USC 262(m)). That meant, for example, that although the incentives of the Orphan Drug Act already applied to biologics, sponsors that completed studies requested under BPCA could now qualify for 6 months of pediatric exclusivity to be added to the 7-year period of orphan drug exclusivity.

However, as explained in Chapter 3, by statute, patents on products with BLAs cannot be extended by pediatric exclusivity. Moreover, supplemental BLAs involving a non-structural change (such as the approval of a new indication) or a structural change that does not change the product's safety, potency, or purity are not eligible for an additional period of exclusivity. Although sponsors of small-molecule drugs are eligible for such exclusivity for certain supplemental NDAs, the periods of exclusivity for drugs described in Chapter 3 (5 years for NDAs for new molecular entities and 3 years for qualifying supplemental NDAs) are relatively short compared to the 12-year exclusivity provided for biologics.

BPCIA presents a host of complicated issues and questions for FDA to consider in developing regulatory guidance and otherwise implementing the legislation. In November 2010, the agency held a public meeting to obtain views on a number of these issues (75 FR 61497). For example, the agency noted that the legislation had altered the definition of biologic by extending it expressly to proteins (excluding chemically synthesized polypeptides).[4] After explaining that there was an "absence of scientific consensus on the distinction between the categories of 'protein' and 'polypeptide' or 'peptide'" (75 FR at 61499), FDA asked for comments on the scientific and technical factors that it should take into account if it develops definitions of these new elements in the definition of biologics. Among several other questions, the agency also asked for comments on factors to consider in determining when a product is highly similar and in deciding what clinical and other studies would be needed to assess differences between a reference product and a proposed biosimilar product.[5]

In the public notice for the meeting, FDA did not ask for comments on pediatric exclusivity. However, in response to a question, a presenter for the American Academy

[4] The legislation specifies that products in this class must now be approved under the PHS Act rather than the FDC Act. An exception provides that certain products that had previously been approved under the FDC Act could still be approved under that act (through March 2020), unless a product in the same class had been approved under the PHS Act and could be considered a reference product.

[5] As this report was being completed in February 2012, FDA issued three draft guidance documents on biosimilars: *Scientific Considerations in Demonstrating Biosimilarity to a Reference Product*; *Quality Considerations in Demonstrating Biosimilarity to a Reference Protein Product*; and *Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009* (see FDA news release at http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm291232.htm).

of Pediatrics noted that the sponsor of an existing biological product would have no incentive to respond to a written request if the standard for approval of a biosimilar product was so high that no approval (i.e., no competition) would be expected (Bromberg, 2010). In an August 2011 commentary on the legislation and the challenges of reconciling law and science, senior FDA officials indicated that FDA was still considering what data would be needed to make the assessments required under the law and to develop regulatory standards (Kozlowski et al., 2011).

Aside from clarifying issues related to biosimilar products, which may affect the strength of the pediatric exclusivity incentive, it is important for FDA to clarify how the exclusivity provision of BPCIA will be applied to biologics that were already approved or under review when the law was passed. In a presentation to the IOM in December 2010, agency staff indicated that they did not expect that many, possibly any, products would soon be candidates for written requests (Ross, 2010). As of December 2011, no requests for studies of biologics had been issued. At that time, FDA was still considering how to implement the exclusivity provisions of BPCIA and was unable to discuss with the committee the law's application to previously approved or submitted products.

For example, would a biologic approved a year before passage of the law, be considered to have 4- and 12-year exclusivities dating from that approval? Would such a product be eligible for a written request and corresponding pediatric exclusivity? The relevance of BPCIA as an incentive for pediatric studies will clearly depend on how the agency interprets the law's provisions.

Even if FDA had determined early on that the incentives of pediatric exclusivity were available to previously marketed biologics, it would still be premature to assess the impact of the law on pediatric studies of biologics. For example, if FDA had quickly issued and sponsors had promptly accepted written requests for pediatric studies of biologics under BPCIA, it would take time for such studies to be planned, completed, analyzed, and submitted to FDA and for FDA to evaluate the studies and make its decision public. For most pediatric studies of safety and effectiveness, this process normally takes several years (except when requested studies have been completed or are under way at the time that the request was issued). Thus, it is highly unlikely that this process for a biologic could have occurred within the period of the IOM study, which was required to start by September 2010.

In sum, given the combination of the legislation's recent adoption, its complexity, the lack of clarity from FDA about the application of pediatric exclusivity to previously approved products, and the typical time horizon for conducting requested studies, the timetable for this IOM study did not allow an assessment either of the number and importance of biological products for children being tested as a result of BPCIA or of the labeling changes made as a result of such testing. Likewise, it is too early to assess the incentives of BPCIA and make recommendations that take into account the law's effectiveness as one means of ensuring pediatric testing of biologics.

Beyond the incentives potentially provided by BPCIA and BPCA, the committee identified two other relevant policies that are not aimed narrowly at pediatric studies. They are the Orphan Drug Act and, potentially, priority review vouchers. As discussed below, the former has encouraged pediatric studies of drugs and biologics for rare diseases. In addition, although PREA establishes requirements rather than providing

incentives for pediatric studies, its provisions are important to any consideration of strategies for ensuring that such studies are conducted when appropriate.

Orphan Drug Act

As described in Chapters 1 and 3, the Orphan Drug Act provides incentives for studies of rare diseases. The law defines a rare condition as one that affects less than 200,000 individuals in the United States. The orphan drug incentives, which include 7 years of exclusivity following the approval of a product for an indication with an orphan designation, are intended to encourage development of new therapeutics. The incentives of BPCA focus on encouraging pediatric studies of products that are already approved for use by adults or for which approval for adult use is the primary development objective. Unlike pediatric exclusivity, the incentives of the Orphan Drug Act are available even for products that have no remaining patent life or other exclusivity.[6]

According to FDA, of the 358 products with orphan drug approvals as of July 2010, almost 20 percent of the approvals involve conditions that exclusively affect children and more than 55 percent involve conditions that affect both children and adults (Goodman, 2010b; personal communication, Catherine Lee, Office of Pediatric Therapeutics, FDA, August 12, 2011).[7] Overall, from 1984 through 2008, biologics approved with orphan designations accounted for about 31 percent of all original BLAs, whereas drugs so designated accounted for 21 percent of approved new molecular entities (calculated from data of Coté, 2009).

Products with orphan designations are exempt from PREA requirements. Thus, when FDA approved Factor XIII concentrate (human) (Corifact) in 2011 for routine prophylactic treatment of congenital Factor XIII deficiency in adult and pediatric patients, the change for this orphan-designated indication was appropriately not attributed to PREA (Vanco, 2011).

When products with orphan designations receive FDA approval, sponsors may agree to conduct postmarket pediatric studies that are not related to requirements under PREA. For example, when alglucosidase alfa (Myozyme) was approved in 2006 for treatment of infantile-onset Pompe disease (a rare enzyme deficiency disease with an orphan designation), the sponsor agreed to complete a postmarket safety and efficacy study with patients with juvenile- and adult-onset disease (Beitz, 2006a).

FDA has sometimes shown considerable flexibility in accepting evidence of efficacy for products to treat rare diseases (Kesselheim et al., 2011). In the case of the just-mentioned alglucosidase alfa, for example, the primary evidence of efficacy was from a randomized, open-label, historically controlled trial involving 18 children with infantile-onset disease (Beitz, 2006a). Although the number of participants was small, the

[6] In addition to exclusivity incentive, the Orphan Drug Act also provides grants to support research on rare conditions. For example, under this program, FDA joined with NIH and the sponsor to fund a pediatric study of peginterferon alfa-2a (Pegasys)/ribavirin (Copegus) combination for treatment of hepatitis C (http://www.accessdata.fda.gov/scripts/opdlisting/oopdgrants/OOPD_Grants_Results_2.cfm). In 2011, FDA approved extension of labeling for the product to cover children ages 5 to 17 years (Birnkrant, 2011).

[7] By November 2011, FDA listed 390 orphan drug approvals at its orphan drug website (http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm).

differences in outcome were substantial. For the treated infants, the ventilator-free survival rate was 83 percent at 18 months, whereas the rate was 2 percent for the 61 patients in the comparison group. The sponsor also agreed to conduct long-term studies to collect growth and development data for children with the condition. (This product is listed in the tables in Appendix D.)

FDA staff have described some concerns about the evidence submitted in support of orphan drug approvals (Pariser, 2010). These concerns included inadequate early-phase dosing and safety studies as a basis for Phase III trials (an issue also identified in this report) and failure to plan and design National Institutes of Health (NIH)-funded therapeutic trials for products for rare diseases so that they would meet FDA criteria for marketing approval. In 2010, another IOM committee recommended that NIH and FDA cooperate on steps to ensure that NIH-supported studies of the pharmacokinetics, safety, or efficacy of drugs for rare diseases are designed and conducted to meet FDA standards (IOM, 2010). Similar cooperation is important when NIH supports other relevant clinical studies of drugs for pediatric use, including studies conducted outside the NIH BPCA program (see Chapter 3).

Priority Review Vouchers

Priority review vouchers, which were authorized under FDAAA, entitle a company that secures FDA approval of a product to treat or prevent specified tropical diseases to obtain expedited FDA review of another product. A company may use the voucher or transfer it to another company. The goal for a priority review is the completion of FDA's review of the New Drug Application or BLA submission within 6 months rather than within the standard 10 months (CDER/CBER, 2008). Somewhat offsetting the value of savings in time, FDA charges a fee for priority review, in addition to other fees that sponsors pay.

Congress is considering a proposal to make priority review vouchers available for studies of rare pediatric diseases (S. 606, Creating Hope Act of 2011; see also BVGH, 2011). Among other features, the proposal would also remove current limits on the transfer or trading of vouchers.

As of June 2011, only one priority review voucher had been redeemed, and that was for a product that clearly had been in development before the creation of the voucher incentive (Moe et al., 2011). The product, artemether/lumefantrine (Coartem), was approved for treatment of acute, uncomplicated malaria in adults and children who weigh 5 kilograms or more (Cox, 2009). Until additional experience with this program accumulates, it is difficult to judge its potential as another incentive for pediatric studies for either drugs or biologics.

Pediatric Rule and PREA

In the absence of incentives under BPCA and in addition to the incentives provided by the Orphan Drug Act, PREA and its predecessor, the Pediatric Rule, have helped to ensure pediatric studies of biologics. Unfortunately, their contributions are not

as clear as they might be. Despite a committee request, FDA could not identify all labeling changes for biologics that were associated with studies required under PREA or the Pediatric Rule (which took effect April 1, 1999). (As explained in Appendix A, FDA's posted table of labeling changes associated with BPCA and PREA did not, until recently, note that it did not include some biologics approved before September 27, 2007.) The committee also could not identify the percentage of biologics approved since 1999 for which either the requirements for pediatric studies were fulfilled from the outset or for which pediatric studies were deferred.[8] In addition, given the incomplete documentation, particularly for biologics approved before 2003, it is possible that some waived or deferred studies that were to have been conducted under the Pediatric Rule or PREA were not identified. For the two dozen new and supplemental BLAs that the committee reviewed for the period from 2008 through 2010, all but one of the letters approving a new indication or other covered labeling change included a statement about pediatric study requirements (e.g., that they had been fulfilled or were deferred). The other letter (Golding, 2008a) approved an indication (chronic inflammatory demyelinating polyneuropathy, for intravenous immune globulin [Gamunex-C]) that the committee found had an orphan drug designation and thus an exemption from PREA requirements.

The discussion below documents a considerable pursuit of pediatric investigations of biologics. The incentives of the Orphan Drug Act have likely motivated some of the completed and ongoing studies, and the requirements of PREA or the Pediatric Rule account for others. Undoubtedly, the promise of many biologics to treat or prevent illness in children is a key motivation for many of the pediatric studies.

Under the circumstances, it seems unlikely that the incentives provided by BPCIA (if applied to previously marketed as well as new biologics) would lead to a surge of written requests for pediatric studies of biologics similar to the surge in requests for pediatric drug studies that followed the creation of the pediatric exclusivity incentive in 1997 (see Chapter 7). Nonetheless, the incentives would likely encourage further studies of some biologics and lead to the addition of information (and an indication) to product labeling. It is reasonable for Congress to continue the incentives until they can be systematically evaluated.

IDENTIFYING BIOLOGICS NOT STUDIED WITH CHILDREN

Defining the Universe of Products

Before the committee could review and assess "the number, importance, and prioritization of any biological products that are not being tested for pediatric use," it had to define the universe of such products. Identification of all biologics, including those that are under development but that are not approved by FDA, was not feasible. Although FDA may have received Investigational New Drug (IND) applications for products under development, FDA does not make INDs public. For older products approved by FDA

[8] Of the 97 biologics that the committee examined, 16 were approved before the Pediatric Rule became effective.

before about 1997, relevant clinical reviews, product labels, and other documents that might describe pediatric studies are rarely public.

At the suggestion of FDA, the committee's review targeted products with BLAs approved by FDA from 1997 through 2010, excluding products that are no longer marketed.[9] From this group of biologics, the committee excluded nontherapeutic biologics such as assays and reagents (e.g., products used for blood testing or blood grouping). It also excluded preventive vaccines, which are often intended primarily or entirely for use by children. Vaccines are the subject of other government policies and programs (e.g., the National Vaccine Program and the Advisory Committee on Immunization Practices) that promote and monitor pediatric (and adult) vaccine development, testing, and improvement. Appendix D provides summary information on pediatric labeling and pediatric studies of vaccines.

With FDA's agreement, the committee concluded that it did not make sense to identify only products that are currently being tested for pediatric use. Rather, the conclusion was that the committee should also attempt to identify biologics for which pediatric studies are either completed or pending. Completed studies might have been submitted for FDA approval and have led to the labeling of a product for children or, at least, to the inclusion of some information from the studies in the labeling. Pending studies might include PREA-required or NIH-supported studies that have not yet started enrolling children. Thus, by identifying completed, ongoing, or pending pediatric studies of biologics, the committee would, by elimination, identify biologics approved since 1997 that (1) had not been studied with children, (2) were not currently under study with children, and (3) were not pending the start of a pediatric study.

Sources of Data

For biologics that are now reviewed and approved by the Center for Drug Evaluation and Research (CDER), FDA staff created and supplied a list of products that were approved from 1997 through 2010. The Center for Biologics Evaluation and Research (CBER) originally approved some of these products before FDA transferred the responsibility for certain categories of therapeutic biologics to CDER in 2003. For biologics that are still under the jurisdiction of CBER, the committee compiled a list of products that had BLAs that were approved from 1997 through 2010 and for which CBER had posted some supporting documents (e.g., approval letters). CBER staff checked this list. The lists were reviewed further to exclude products that were approved before 1997, were approved under new drug applications (NDAs), were not approved for marketing in the United States, had been withdrawn from the market, or were not new products. The final list included 97 biologics, 58 of which are now regulated by CDER, and 39 of which are now regulated by CBER.

To identify biologics that had been studied, were being studied, or were planned for study with children, the committee consulted several sources of information, including

[9] Because the biologics included are limited to those with BLAs, they exclude certain animal-derived or recombinant products that were approved under the NDA rather the BLA process (see note 3 earlier in this chapter).

- the current product labeling;
- the product approval letter(s), if available;
- the FDA database that tracks various kinds of postmarket study requirements or commitments, including those required under PREA; and
- clinicalTrials.gov, an NIH-administered registry of publicly and privately supported clinical trials.

It also consulted with CBER staff. For products for which no pediatric studies were identified in the sources described above, the committee searched further for pediatric studies in PubMed, the National Library of Medicine's database of biomedical literature citations and abstracts.

Current Product Labeling

The first step in identifying completed pediatric studies was a search of a product's current labeling for approved pediatric indications; references to pediatric pharmacokinetic, safety, or efficacy studies; or statements indicating that the product had not been studied with children. According to FDA, the statement in the labeling of a CBER-regulated product that "safety and efficacy have not been established in pediatric patients" means that the products had not been studied with children (personal communication, Catherine Lee, Office of Pediatric Therapeutics, FDA, August 8, 2011). The committee also searched for warnings or recommendations against use with children that were based on analyses of adverse event reports. In most cases, the labeling consulted was that posted by the sponsor; FDA did not always have the current label posted.

Some product labeling is ambiguous about pediatric studies. For example, the label for crotalidae polyvalent immune Fab (ovine) (CroFab) states that "specific studies" of pediatric patients have not been conducted, but the label also describes two clinical trials conducted with individuals 11 years old or older (Protherics, Inc., 2010, unpaged). The pediatric use section of the labeling for antithymocyte globulin (rabbit) (Thymoglobulin) states that "safety and efficacy have not established in controlled trials" but goes on to state that dose, efficacy, and adverse event profile "are thought to be similar to adults" on the basis of limited (presumably uncontrolled) European studies and other data (Genzyme, 2008, unpaged). Because studies of both products are listed in the clinical trials database discussed below, they are categorized to have been studied with children.

Labeling is also ambiguous for Rho(D) immune globulin intravenous (Rhophylac). It is labeled for suppression of Rhesus (Rh) isoimmunization in pregnancy and obstetric conditions and in incompatible transfusions in Rho(D)-negative individuals and also for raising platelet counts in Rho(D)-positive, non-splenectomized adults with chronic idiopathic thrombocytopenic purpura (ITP). The use of the term "individuals" for one indication and "adults" for another indication could reasonably be interpreted as implying that the term *individuals* referred to individuals of all ages. However, the labeling later states that the safety and effectiveness of the product have not been

established in pediatric subjects being treated for an incompatible transfusion but also that the physician should weigh the potential risks against the benefits of treatment, particularly for girls whose later pregnancies might be affected by Rh isoimmunization. The 2007 labeling posted by CBER includes a statement that "studies have demonstrated the safe and effective use of Rho(D) Immune Globulin in children with ITP" (CBER, 2007, unpaged). However, the latest manufacturer's labeling, which has not been posted by CBER, does not include that statement (CSL Behring, 2010). As described in Box 8-2, a similar product, WinRho, is labeled for pediatric use for ITP.[10] Because no pediatric studies are listed at ClinicalTrials.gov for RhoPhylac (by brand name) and the current labeling is ambiguous and does not cite pediatric studies, the product is categorized as not labeled for use by children and not studied in children.

Approval Letters and Postmarket Study Requirements Database

In addition to consulting the product labeling, the committee reviewed FDA approval letters in the public domain for references to studies required under the Pediatric Rule or PREA. These letters may indicate that the sponsors have fulfilled the requirement for some or all age groups, that FDA is deferring pediatric studies because products are ready for approval for adults, or that the product is exempt from PREA requirements because it has an orphan drug designation. FDA may also waive PREA requirements for some or all age groups, for example, because the indication approved is rare or not found in children. (The committee counted seventeen biologics that either were approved before April 1, 1999, when the Pediatric Rule became effective or were approved during the period between October 17, 2002, and December 2, 2003, i.e., after the Pediatric Rule had been overturned by the courts but before PREA was enacted.)

Approval letters for biologics do not always refer to the requirement for pediatric studies. In these cases, the committee checked to see whether sponsors had pediatric labeling from the outset or had orphan drug designations for the indications cited in the letters. It also checked FDA's postmarket requirements and commitments-tracking website to see whether any PREA requirements were listed there.[11]

[10] In addition to the ambiguous labeling, another source of confusion is that CBER has not posted the most recent labeling (package insert) for either of these products, although the current labeling can be found at the manufacturers' websites. The CBER website indicates the information posted for licensed biological products with supporting documents includes the current package insert. (http://www.fda.gov/BiologicsBloodVaccines/ucm133705.htm).

[11] As described in Chapter 3, the FDA Modernization and Accountability Act of 1997 (FDAMA; PL 110-95) required sponsors to report annually on their progress in meeting postmarket study requirements. It likewise directed FDA to provide annual summaries based on these reports. The current website allows a status search by product and type of requirement (http://www.accessdata.fda.gov/scripts/cder/pmc/index.cfm).

Clinical Trials Registry

For many biologics, ClinicalTrials.gov lists pediatric trials that appear to match studies that have already been submitted to FDA or that have been required in approval letters.[12] Some listings describe pediatric studies for conditions for which a product has neither an approved adult indication nor a pediatric indication.[13]

Although the ClinicalTrials.gov database allows searches by age category "child (birth–17)" (meaning up to age 18 years, as other usage makes clear), the summary search listings are not particularly reliable. Notably, if the more detailed description of study eligibility criteria does not have an entry for "ages eligible for study," that study will be included in the summary search results for "child" studies, even if the eligibility criteria in the study's detailed description refer to a minimum participation age of 18 years or otherwise make clear that the study does not include children. For example, a search for "becaplermin" (Regranex) and "child" generates a listing for the study "Becaplermin Use and Cancer Risk in a Patient Population of U.S. Veterans with Diabetes" (ClinicalTrials.gov identifier: NCT01235260); the summary describes the age group to be "child/adult/senior." In a few instances, study descriptions specified the lower age range for study eligibility to be 16 years. The committee did not consider these pediatric studies; no products were classified to have not been studied with children as a result of this decision.

For some categories of biologics, in particular, the intravenous immune globulin (IVIG) and antihemophilic products, summary descriptions of trials often do not identify the specific products being studied by brand name. Search results may include a listing that, in fact, describes a study of a product other than one identified to be a search term. Including the product's sponsor as a search term may exclude studies of competitors' products but may also exclude potentially relevant studies of the product funded by other entities. For example, restricting the search for IVIG products to studies of a product's sponsor would have excluded the National Institute of Mental Health study of the IVIG product (Gamunex) for treatment of pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (ClinicalTrials.gov identifier: NCT01281969). Given the difficulty of identifying these kinds of individual products in the database, the

[12] In 1997, FDAMA required the creation of the clinical trials database to provide information about certain interventional studies of drugs, biologics, and devices (Phases II through IV) for which FDA has issued an IND Application or an Investigational Device Exemption or for which there was at least one U.S. study site. FDAAA expanded the scope of the database, for example, by requiring the reporting of results for certain trials. Sponsors may also register trials for which FDA does not require registration (e.g., Phase I trials). The National Library of Medicine of the National Institutes of Health administers the database (http://clinicaltrials.gov/ct2/info/about). In addition to the FDA requirements, the International Committee of Medical Journal Editors requires prior registration as a condition for publication of articles about covered clinical trials (Laine et al., 2007).

[13] Searches sometimes yielded listings that did not involve a clinical trial of the product. For example, the description of an NIH study of antibody production in immune disorders noted that participants would be asked, among other questions, about use of IVIG products (ClinicalTrials.gov identifier: NCT00023504). This type of study was excluded.

analysis of the trials database grouped a few classes of biologics together for analysis (see Appendix D).[14]

The tables in Appendix D may understate the extent of pediatric studies for some products because the committee did not attempt a comprehensive search of the broader scientific literature for all products. Such a search might have identified older studies that predate the clinical trials registry and that were not pursued to support labeling in the United States.

Results: Products Studied with Children

Table 8-1 summarizes the primary results of the committee's search. Tables D-1 and D-2 in Appendix D provide detailed information for 97 still-marketed products that were approved by FDA from 1997 through 2010.

TABLE 8-1 Summary Information on Biologics Studied in Children[a]

	No. (%) of Biologics		
Data Source	All (*n* = 97)	CDER (*n* = 58)	CBER (*n* = 39)
Products with pediatric information in most recent labeling[a]	58 (60)	30 (57)	28 (72)
Products with registered pediatric trials[b]	82 (85)	51 (88)	31 (80)
Summary: Products with pediatric information in labeling or registered pediatric trials or both	85 (88)	51 (88)	34 (87)

NOTE: Biologics included were originally approved by FDA from 1997 through 2010. See Appendix D for more details.

[a] Labeling (as of July 2011) (1) includes a pediatric indication or mentions pediatric studies or both or (2) includes an explicit warning about lack of pediatric safety.

[b] Data at ClinicalTrials.gov were consulted between August and November 2011 for plausible listings of pediatric studies. Plausible listing means that the description of the study, even if it did not mention the product by name, suggests that it is likely to be a study of the product, for example, because the company funding or sponsoring the study is the company that sponsored the BLA (or its successor company).

SOURCE: Tables D-1 and D-2, Appendix D.

In general, Table 8-1 presents a positive picture. For approximately 60 percent (*n* = 58) of biological products, the labeling includes a pediatric indication for at least one pediatric age group or information from pediatric studies, or both, or it includes a specific warning about a lack of safety on the basis of FDA analysis of adverse event reports or

[14] FDA does not treat these products as interchangeable for purposes of marketing approval, but hospital formularies, clinicians, and health plans may. The committee did not examine or take a position on this practice. Differences in IVIG products that may be clinically relevant include their purification processes, concentration, stabilizing agents, and pH (http://www.ashp.org/s_ashp/docs/files/DShort_IVIGsidebysideupdatedDec07.pdf).

other data. Of these products, 43 were considered to be labeled for pediatric use, although the labeling, particularly for the older biologics, is not always explicit. For products not labeled for pediatric use, the labeling may report pharmacokinetic or safety information from pediatric studies, including studies that did not demonstrate safety or efficacy.

Products with pediatric study information in the labeling may have been intended from the outset to be approved for use by children (e.g., clotting factors and enzyme replacement therapies), or studies of the products may have been conducted in response to PREA requirements or orphan drug incentives. Some products with no information about pediatric studies in the current label may have information added in the future, for example, as a result of studies now under way or planned. For other products, studies now planned or under may be stopped or not pursued further on the basis of safety findings or results showing a lack of activity or efficacy. For studies not required under PREA, such negative safety or efficacy results might not be reflected in the product's labeling. In some cases, changes in the priorities of sponsors may affect their pediatric research program.

Biologics with waivers of pediatric studies or orphan drug exemptions may still be evaluated in studies with children (Box 8-1). Some products may have waivers for one indication but not another, and as noted earlier, a majority of orphan drugs are approved for conditions that affect children.

BOX 8-1
Examples of Products with PREA Waivers or Orphan Designation Exemptions for Which Pediatric Studies Are Listed at ClinicalTrials.gov

Alpha1-Proteinase Inhibitor (Human) (GLASSIA) (BLA 125325): approved in 2010, one of several products approved for treatment of emphysema due to a congenital deficiency of α_1-proteinase inhibitor. The CBER approval letter waived the requirement for pediatric studies because this deficiency "is not known to cause emphysema in pediatric subjects" (Malarkey and Epstein, 2010). The sponsor has registered a randomized, placebo-controlled, Phase II study of the safety and efficacy of an investigational inhaled formulation of the product in individuals (ages 5 years and older) with cystic fibrosis (ClinicalTrials.gov identifier: NCT00499837). In 2004, the sponsor received orphan designation for this indication, and the sponsor of another product in this class (CSL Behring) has likewise obtained such a designation, although no apparently related studies are registered for the latter company. In addition, the sponsor of GLASSIA has registered a Phase I/II trial of the product as a possible disease-modifying agent in type 1 diabetes mellitus; enrollment criteria specify ages 10 to 25 years inclusive (ClinicalTrials.gov identifier:NCT01304537). In 2011, the sponsor obtained an orphan designation for treatment of recent-onset type 1A diabetes mellitus with residual beta-cell function in children less than 15 years of age. Pediatric studies of diabetes have been registered for at least one other similar biologic (Aralast NP) with the same approved indication (see, e.g., ClinicalTrials.gov identifier: NCT00499941).

Antithrombin (Recombinant) (ATryn) (BLA 125248): approved in 2009 for the prevention of perioperative and peripartum thromboembolic events in patients with hereditary antithrombin deficiency. FDA determined that it was exempt from pediatric study requirements based on the orphan designation of that indication (Malarkey and Epstein, 2009). The sponsor has a Phase I

study registered to investigate the use of the products with neonates scheduled for surgery involving cardiopulmonary bypass (ClinicalTrials.gov identifier:NCT01158729).

Rimabotulinum-Toxin B (Myobloc) (BLA 103846): approved in 2000 for treatment of cervical dystonia in adults. That indication has an orphan drug designation dating to 1992. In 2005, the sponsor registered a Phase I/II trial to investigate whether the product could improve hand functioning for children with upper-extremity hypertonia (stiffness of the arm) related to cerebral palsy (ClinicalTrials.gov identifier:NCT00238641). The study, which is listed as completed but without posted results, was to have enrolled 10 children from the ages of 2 up to 18 years.

Romiplostim (Nplate) (BLA 125268): approved in 2008 for treatment of thrombocytopenia in patients with chronic immune thrombocytopenic purpura who have had an insufficient response to certain other treatments. The product was exempt from pediatric study requirements because it had an orphan drug designation for the indication (Pazdur, 2008). The sponsor conducted a Phase I/II randomized, double-blind safety and efficacy study of the drug for treatment of thrombocytopenia in pediatric subjects ages 12 months up to 18 years with immune (idiopathic) thrombocytopenic purpura (ClinicalTrials.gov identifier: NCT00515203). Reports on the completed study claimed that it showed that the product was well tolerated and effective (Buchanan et al., 2009; Bussel et al., 2011).

SOURCES: Tables D-1 and D-2 in Appendix D and ClinicalTrials.gov. Information about orphan drug designations and approvals can be found at http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm.

The committee did not systematically categorize pediatric labeling, PREA requirements, or registered studies by age groups. For some products, it is possible that a public health benefit might accrue from investigations with individuals in age groups not yet studied. For example, in 2009, after the 1-year safety review for a fibrin sealant (Artiss), the Pediatric Advisory Committee recommended that the product, which is labeled for use with other children, be studied in infants less than 1 year of age (PAC, 2009). FDA had previously waived studies related to skin grafts for burns for that age group (Epstein, 2008).

Results: Products Not Studied with Children

Overall

Although a sizable majority of biologics have been studied, are being studied, or are planned for study with children, the resources that the committee consulted showed no indication that pediatric studies had been completed, are under way, or are pending recruitment for a few products. Box 8-2 lists the 12 products for which no pediatric studies were identified in the product labeling, the approval letter(s) (or FDA's tracking database for study requirements or commitments), or the clinical trials registry. The table also indicates whether the committee found citations relevant to pediatric study of the product in PubMed. As discussed below, the first product listed in Box 8-2 appears to be a possible candidate for consideration for study with children.

BOX 8-2
Products with No Indication of Pediatric Studies in Labeling, FDA Approval Letters, or Clinical Trials Registry (ClinicalTrials.gov)

Possible Candidate for Pediatric Study

Becaplermin (Regranex) (BLA 03691): approved in December 1997 for treatment of lower extremity diabetic ulcers. A 2005 labeling change added information about studies with adults that did not demonstrate efficacy for treatment of for pressure ulcers and venous stasis ulcers. At that time of that change, FDA granted a waiver of required pediatric studies for all age groups (the rationale was not stated). PubMed lists a report of a retrospective case series analysis of use of the product to treat ulcerated hemangiomas of infancy (Metz et al., 2004).

Products with no Pediatric Studies Identified but Closely Related Products Are Labeled or Studied for Pediatric Use

Alpha$_1$ Proteinase Inhibitor (Human) (Zemaira) (BLA 125078): approved in July 2003 for treatment of individuals with alpha$_1$-proteinase inhibitor deficiency and evidence of emphysema. No pediatric studies are listed at ClinicalTrials.gov, but pediatric studies involving similar products are listed in that database, including studies of cystic fibrosis and type 1 diabetes (see the first entry in Box 8-1).

Digoxin Immune Fab (Ovine) (DigiFab) (BLA 103910): approved in August 2001 for treatment of patients with life-threatening or potentially life-threatening digoxin toxicity or overdose. The approval letter does not mention waived or deferred pediatric studies, and no deferred studies are listed at the tracking database for postmarket study requirements. The product's labeling notes that a similar product has successfully been used to treat infants, as does the label for that product, Digibind (which was approved by FDA in 1986 with an orphan drug designation). Among other similar citations for studies of the latter product listed in PubMed, a 1991 article abstract describes positive results for efficacy and safety from the analysis of 57 pediatric cases gathered as a result of the multicenter clinical trial and postmarket surveillance study (Woolf et al., 1991).

Incobotulinumtoxin A (Xeomin) (BLA 125360): approved in July 2010 for treatment of cervical dystonia and blepharospasm (eyelid twitch). FDA waived pediatric study requirements for all age groups for both indications because too few children were available for study participation. Other botulinum products have been studied with children. One product, onabotulinumtoxin A (Botox) is approved for pediatric use for blepharospasm or strabismus for patients 12 years of age and older. According to FDA's database of postmarket study requirements and commitment, this product is also the subject of PREA requirements for upper limb spasticity (ages 2 up to 17 years), severe axillary hyperhidrosis, prophylaxis of headaches with chronic migraine (in adolescents ages 12 to 17 years), and urinary incontinence due to detrusor overactivity associated with a neurologic condition. Pediatric trials involving the product are registered for additional conditions, including cerebral palsy and clubfoot. A second product, abobotulinumtoxin A (Dysport) is not labeled for pediatric use, but trials are registered for studies with children with lower limb spasticity and possibly other conditions. The labeling for all three products includes a boxed warning of the risk that the effect of the toxin could spread from the injection site and cause swallowing and breathing difficulties and death. The symptom reports that prompted the warning mostly involved children with cerebral palsy (FDA, 2009d).

Ranibizumab (Lucentis) (BLA 125156): approved in June 2006 for treatment of neovascular (wet) age-related macular degeneration and in June 2010 for treatment of macular edema following retinal vein occlusion. FDA waived required pediatric studies without explanation for the first indication and waived required pediatric studies for the second indication because studies would be impossible or highly impracticable as too few pediatric patients with macular edema following a retinal vein occlusion exist. Another antivascular endothelial growth factor product (bevacizumab [Avastin], approved in February 2004) from the same sponsor is registered for a study of treatment of retinopathy of prematurity and for several pediatric cancer studies. Ranibizumab is a fragment of the bevacizumab antibody. Case reports of the use of ranibizumab listed in PubMed describe use of the product with children for treatment of choroidal neovascularization of various origins (Benevento et al., 2008; Goodwin et al., 2009; Gregory-Evans, 2009; Kohly et al., 2011). Bevacizumab, which is approved for treatment of several types of cancer, is widely used off-label and at lower cost for neovascular age-releated macular degeneration; preliminary results from a controlled trial show similar outcomes for both products according to a recent government report (OIG/HHS, 2011).

Rho(D) Immune Globulin Intravenous (*Rhophylac*) *(BLA 125070):* approved in February 2004 for suppression of rhesus (Rh) isoimmunization in Rho(D)-negative individuals transfused with transfused with Rho(D)-positive red blood cells or blood components. (See discussion of the ambiguous labeling of this product earlier in this chapter.) FDA waived required pediatric studies for this indication (Golding, 2004). According to the manufacturer's current labeling, in March 2007, FDA approved the product for treatment of immune thrombocytopenic purpura in adults (CSL Behring, 2010). The 2007 approval letter is not public, but no postmarket studies are listed in FDA's tracking database. Several pediatric studies of this type of product (also called Anti-D Immune Globulin) are registered at ClinicalTrials.gov or listed in PubMed, but none are listed under the brand name Rhophylac. Another Rho(D) immune globulin intravenous (human) product, WinRho, which was originally approved in 1995, is labeled for use for idiopathic thrombocytopenic purpura in adults and children and for suppression of Rh isoimmunization (including in girls and women) (Cangene, 2010). ClinicalTrials.gov lists a pilot study of this product for dengue fever (ClinicalTrials.gov identifier: NCT01443247), and a study listed at PubMed shows interim results from a study in adults and children for thrombocytopenia in dengue fever (de Castro et al., 2007). A listing of registered studies for "anti-D" (with no brand identified) included a pediatric study for idiopathic thrombocytopenic purpura (ClinicalTrials.gov identifier: NCT00128882).

Other Biologics Not Identified to Have Been Studied with Children

Autologous Cultured Chondrocytes (Carticel) (BLA 103661): approved in August 1997 for repair of cartilage defects of the femoral condyle caused by acute or repetitive trauma in patients who have had an inadequate response to a prior arthroscopic or other surgical repair procedure. No pediatric studies were identified at ClinicalTrials.gov or PubMed.

Collagenase Clostridium histolyticum (Xiaflex) (BLA 125338): approved in February 2010 for treatment of Dupuytren's contracture with an orphan designation for that indication and an exemption from PREA requirements. No pediatric studies were identified at ClinicalTrials.gov or PubMed.

Interferon Alfacon-1 (*Infergen*) *(BLA 103663):* approved in October 1997 for treatment of chronic hepatitis C and in 2010 for use in combination therapy for the same condition. In 2010 FDA waived required pediatric studies on grounds that the product does not offer a meaningful therapeutic benefit over current therapies and is unlikely to be used by a substantial number of pediatric patients. No pediatric studies were identified at ClinicalTrials.gov or PubMed.

Pegloticase (Krystexxa) (BLA 125293): approved in September 2010 for treatment of chronic gout refractory to conventional treatment. It has an orphan drug designation for this indication and is thus exempt from PREA requirements. No pediatric studies were identified at ClinicalTrials.gov or PubMed.

Sipuleucel T (Provenge) (BLA 125197): approved in April 2010 for treatment of prostate cancer with a PREA waiver because the condition is unlikely to occur in the pediatric population. No pediatric studies were identified at ClinicalTrials.gov or PubMed.

Tositumomab and Iodine I 131 Tositumomab (*Bexxar*) *(BLA 125011):* approved for treatment of non-Hodgkin lymphoma in June 2003. The approved indication has an orphan designation is thus exempt from PREA requirements. No pediatric studies were identified at ClinicalTrials.gov or PubMed.

SOURCES: Tables D-1 and D-2 in Appendix D.

Most of the products listed in Box 8-2 were approved for treatment of conditions that are not found or are rare in children. FDA has waived pediatric study requirements for some indications (e.g., prostate cancer and diabetic foot ulcers) and exempted studies for others that have an orphan designation (e.g., Depuytren's contracture and chronic gout). For five products for which no pediatric studies were identified, similar products have been tested with children.

One product was approved before the Pediatric Rule took effect and had no subsequent labeling change, and two products were first approved during the hiatus between the overturning of the Pediatric Rule and the passage of PREA effect and had no subsequent labeling changes. Four of the products listed in Box 8-2 were approved in 2010. Possible pediatric applications may emerge as more experience with these products develops.

Product with Possible Promise for Pediatric Study

For FDA, the issuing of a request for a pediatric study under BPCA is to be based on the agency's determination that information about the use of a product by the pediatric population may yield health benefits. Becaplermin (Regranex), a topical platelet-derived growth factor that is approved for treatment of diabetic foot ulcers (with a waiver of required pediatric studies), might yield such benefits for a different condition found in children.[15] The product is the subject of a case series report of eight infants treated with the product for ulcerated perineal hemangiomas of infancy (Metz et al., 2004). Other sources suggest that the product is viewed as an effective off-label option for short-term treatment of refractory infantile hemangiomas when other treatments, including other

[15] According to the European Medicines Agency, the company that distributes the product in Europe announced in 2011 that for commercial reasons (i.e., low demand and availability of alternative treatments) it would cease supplying it as of June 30, 2011 (EMA, 2011). In the United States in 2011, a company that makes other wound care products acquired rights to the product (Robertson, 2011).

products (e.g., beta blockers and corticosteroids) used off-label, have failed (see, e.g., Cohen, 2007; Children's Hospital of Wisconsin, 2010; NOVA, 2010).

FDA or NIH could take several criteria into account in considering whether becaplermin has sufficient potential health benefits (taking risks and alternative treatments into account) to warrant encouraging or supporting controlled pediatric trials. For example, the National Institute of Child Health and Human Development (NICHD) has identified criteria that may be used to guide the setting of priorities for pediatric therapeutics as required under BPCA (see Chapters 1 and 3) (NICHD, 2011; see also Goodman, 2010a). The criteria for evaluating candidate therapies include

- relevance to NICHD's BPCA mission and goals (which primarily involve off-patent products);
- possible disqualifying ethical concerns (e.g., product labeling with a boxed warning);
- gaps in existing evidence;
- potential effects on children (e.g., taking into account prevalence and burden of a condition and the availability of alternative therapies);
- potential effects on society and the delivery of medical care (e.g., taking into account costs and health disparities);
- different populations that might benefit from research; and
- availability of resources (e.g., from private sources) to fund research.

The committee did not attempt a formal assessment of becaplermin against these criteria, for example, by seeking public input. It did identify some information relevant to the above-mentioned criteria that might inform an FDA or NIH decision. First, in 2008, FDA approved the addition of a boxed warning to the product's labeling (FDA, 2008; see also Frieden, 2008). The warning, which was based on data from adults with diabetes who used the product repeatedly for foot ulcers, cited an increased risk of mortality secondary to malignancy and recommended caution in the use of the product for patients with known malignancy. Second, although FDA has not approved any products for treatment of infantile hemangiomas, other products are also being tested for the condition.[16] These products (primarily corticosteroids and beta-blockers) are not biologics and have generic versions, and FDA and clinicians have extensive experience with the safety profiles of these products, including their risks to children. Third, if these products were found to be safe and effective for treatment of refractory hemangiomas, they would likely be less expensive than becaplermin. Fourth, with respect to the condition, infantile hemangiomas of various degrees of severity may be relatively common (e.g., an estimated incidence of 4 to 5 percent overall) (Children's Hospital of Wisconsin, 2010). Depending on where the hemoganioma is located (e.g., the eye or the anal region), it can, if ulcerated, take years to resolve and cause pain, scarring, and other serious problems. Fifth, as described above, becaplermin is being used off-label to treat infants in the absence of controlled studies to evaluate its safety and efficacy.

[16] See, for example, trials with the following ClinicalTrials.gov identifiers: NCT01074437, NCT00967226, NCT01056341, NCT01072045, and NCT01010308.

For five products listed in Box 8-2, the committee identified pediatric studies of similar products. In these cases, FDA or NIH consideration of pediatric studies of the listed product might take into account (1) whether the similar product has pediatric labeling and, if yes, what the risk-benefit profile is for this use and (2) whether evidence of off-label use of the unstudied version of the product suggests a possible health benefit from pediatric studies. If the similar product is not labeled for pediatric use and does not have an IND application, FDA or NIH might investigate the status of the pediatric studies of the products to assess its promise as a possible higher-priority candidate for FDA or NIH support.

CONCLUSIONS

Whether as a result of Orphan Drug Act incentives, requirements under PREA, or other reasons, approximately 60 percent of the 97 still-marketed biologics approved by FDA since 1997 are labeled for pediatric use or have information about pediatric use in the labeling. Most of the remaining products have been studied, are being studied, or are planned for studies with children. This is not to say that no further opportunities or needs for pediatric studies of these products exist. Such opportunities might, for example, involve studies that pursue promising findings from early-phase studies, studies with for additional indications or for individuals in additional pediatric age groups, or long-term studies of safety and effectiveness. If FDA has determined that already labeled or studied products would be eligible for pediatric exclusivity, it might then make written requests to encourage pediatric studies of some products. The priority-setting criteria described in this chapter may help with decision making.

Of the small number of products that have not been studied with children, most appear to have limited potential for pediatric use. It is possible that future research on the mechanism of action of one or more of these products will suggest promising lines of investigation involving pediatric conditions. At this time, on the basis of experience with off-label use, one product may have sufficient promise that FDA or NIH, or both, might consider encouraging or supporting controlled pediatric trials, whether through requests under BPCA or otherwise.

Given the timing of BPCIA and its early stage of implementation, the committee could not practically assess its impact as an incentive for pediatric studies of biologics or make recommendations about its effectiveness. Other policies have, however, had an impact. Since it became effective in 1984, the Orphan Drug Act has encouraged pediatric studies of drugs for rare conditions. Although overall data on PREA-related labeling changes for biologics are not available from FDA, PREA and its predecessor, the Pediatric Rule, have prompted pediatric studies of biologics for conditions that are found in children and are not covered by an orphan drug designation.

As described in Chapter 7, the creation of the pediatric exclusivity incentive in 1997 (effective in July 1998) led to a surge of written requests for pediatric drug studies that peaked in 1999. A peak in exclusivity determinations followed in 2008. It seems unlikely that BPCIA will have a similar impact for biologics. Older biologics have been eligible for the incentives of the Orphan Drug Act, and newer biologics have been subject to PREA determinations. A substantial majority of biologics approved since 1997 have

already been the subject of some type of pediatric study, and some information about these studies is included in the labeling of most of these products. Nonetheless, it is reasonable to expect that the incentives of BPCIA may encourage further studies of some biologics to the benefit of children, and thus, *it is reasonable for Congress to continue these incentives until they can be systematically evaluated 3 to 5 years after FDA issues implementing regulations*.

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A
Study Activities, Methods, and Public Meetings

In late 2009, the Food and Drug Administration (FDA) approached the Institute of Medicine (IOM) about an examination of pediatric studies of drugs and biologics conducted under the provisions of the Best Pharmaceuticals for Children Act (BPCA) and the Pediatric Research Equity Act (PREA) called for in the 2007 reauthorizations of these two acts. In March 2010, as part of the Patient Protection and Affordable Care Act, Congress changed the specifications for biological products to reflect changes elsewhere in the legislation affecting incentives for the development of these products. Taking these revisions into account, FDA asked that an IOM committee

1. Review and assess a representative sample of written requests issued by the Secretary [of the U.S. Department of Health and Human Services] and studies conducted under BPCA since 1997, and labeling changes made as a result of such studies;
2. Review and assess a representative sample of studies conducted since 1997 under PREA or precursor regulations, and labeling changes made as a result of such studies;
3. Using a representative sample of written requests issued by the Secretary and studies conducted under BPCA since 1997 and studies conducted since 1997 under PREA or precursor regulations, review and assess (a) the use of extrapolation for pediatric subpopulations; (b) the use of alternative endpoints for pediatric populations; (c) neonatal assessment tools; and (d) ethical issues in pediatric clinical trials;
4. Using a representative sample of studies conducted since 1997 under PREA or precursor regulations, review and assess the number and type of pediatric adverse events;
5. Review and assess the number and importance of biological products for children that are being tested as a result of the amendments made by the Biologics Price Competition and Innovation Act of 2009 [*sic*][1] and the importance for children, health care providers, parents, and others of labeling changes made as a result of such testing;
6. Review and assess the number, importance, and prioritization of any biological products that are not being tested for pediatric use; and
7. Offer recommendations for ensuring pediatric testing of biological products, including consideration of any incentives, such as those provided under section 505A of the Federal Food, Drug, and Cosmetic Act or section 351(m) of the Public Health Service Act.

[1] This legislation was actually passed in 2010 as part of the Patient Protection and Affordable Care Act.

The 13-member study committee appointed by the IOM met five times between December 2010 and October 2011. Three of these meetings included public sessions during which the committee heard from a range of interested parties, including government officials from FDA and the National Institutes of Health and individuals from organizations representing pharmaceutical and biotechnology companies, pediatricians, researchers, and advocates. The agendas for the public sessions follow this overview of study activities and methods.

The committee also sought assistance from consultants for the preparation of background papers and other analyses to supplement those undertaken by the committee. The consultants are listed after the committee members in the front of this report. The background papers appear as Appendixes B and C, and Appendix D presents information on biologics studied in children, much of which was checked or compiled by a consultant.

The committee's statement of task refers to written requests, studies, and labeling changes that have been made since 1997. However, the provisions of the FDA Modernization Act creating the written request mechanism and the pediatric exclusivity incentive did not go into effect until July 1, 1998, and the effective date of the 1998 Pediatric Rule was April 1, 1999. Therefore, the committee used these dates as the start dates for its sampling of FDA documents. Because FDA may not post relevant documents for some period after the approval of a product or labeling change, the committee chose December 31, 2010, to be the cutoff point for its sample.

FDA supplied the committee with its master list of labeling changes for the specified time period. It also supplied a list of 14 products for which exclusivity had been granted but a labeling change did not occur. The lists characterized the products by therapeutic area and policy origin. Some products had more than one labeling change. Neither the list supplied by FDA nor an online table of labeling changes explained that it omitted changes made before September 27, 2007, for biologics that are regulated under the Public Health Service Act.[2] FDA was unable to supply a list of these omitted labeling changes. Thus, the list supplied to the committee understates to an unknown extent the number of labeling changes made as a result of studies of biologics that were required under PREA.

Prior to the September 27, 2007, reauthorizations of BPCA and PREA, FDA was not required to make public either the clinical, clinical pharmacology, and statistical reviews associated with labeling changes or the written requests associated with the granting of pediatric exclusivity. The IOM could request documents associated with earlier labeling changes and exclusivity determinations, but the FDA could not release them until they had been reviewed and redacted to remove proprietary and other information that FDA considers not releasable.

[2] As the committee was preparing to release the report in February 2012, FDA posted a revised table of labeling changes related to BPCA and PREA. It included an explanation that labeling changes for relevant biological products regulated by the Center for Biologics Evaluation and Research were included in the table beginning September 27, 2007 (but not before that date). Although not noted, the table also omits some and perhaps all biologics that are now regulated by the Center for Drug Evaluation and Research and that had labeling changes prior to the same date (see, e.g., Drugs@FDA for September 2001and December 2005 approval letters for darbepoetin alfa [Aranesp]) and a 2002 letter for rasburicase [Elitek]).

One key question that was discussed over a period of months was whether FDA could agree to a schedule for redacting and releasing requested documents that would allow the IOM time to do its assessments, analyze them, consider the results in developing its report, and stay on schedule to deliver the report. After the committee's second meeting in February 2011, FDA agreed that it would provide requested documents for up to 50 products that are now regulated by the Center for Drug Evaluation and Research. The agreement did not cover products now regulated by the Center for Biologics Evaluation and Research. It also did not cover at least 12 products for which exclusivity was granted without a labeling change.

Because the committee had already selected a sample of products for assessment based on the availability of documents for labeling changes made after September 26, 2007, it had to identify a new sample for the period from July 1, 1998 through December 31, 2010. Insofar as possible, the committee sought to include labeling changes for products for similar clinical indications from three time periods that roughly correspond to different regulatory eras. These periods were

- July 1, 1998–December 31, 2002 (early period, representing the early implementation of the pediatric exclusivity provisions from the FDA Modernization Act of 1997, effective July 1, 1998, and the Pediatric Rule, effective April 1, 1999, but overturned by the courts in October 2002);
- January 1, 2003–September 26, 2007 (middle period); and
- September 27, 2007–December 31, 2010 (recent period, following the reauthorizations of BPCA and PREA in 2007).

Consistent with the provision that the IOM use a representative sample for its assessments, the committee selected products from the major therapeutic areas identified by the Government Accountability Office (which were reported in the list supplied by FDA). These areas, which generally parallel FDA review divisions, were analgesia/anesthesia, anti-inflammatory, cardiovascular disease, dermatology, endocrinology/metabolism, gastroenterology, hematology/coagulation, infectious disease (nonviral), infectious disease (viral), medical imaging, neurology, oncology, ophthalmology, and pulmonary. The committee excluded vaccines from its sample. Most vaccine development programs include studies or expectations of studies with pediatric age groups from the outset. Moreover, the need for vaccines for various diseases and populations is closely monitored by several government agencies, including the National Vaccine Program, the Advisory Committee on Immunization Practices, and the FDA's Vaccines and Related Biological Products Advisory Committee. Appendix D includes a brief description of the extent of pediatric labeling and pediatric studies for vaccines for which FDA has posted some supporting documents. The committee also excluded contraceptive products, which are routinely approved for use by postpubertal adolescents on the basis of extrapolation of safety and efficacy data from studies with adults without pediatric studies. With these exclusions, the universe of relevant labeling changes totaled 381.

In an effort to learn more about how FDA requests or requirements might have changed over time, the committee generally selected products within each therapeutic area with similar indications, for example, juvenile rheumatoid arthritis. After a few older

products with particularly confusing or poorly documented regulatory histories were excluded, the committee's final sample included 46 FDA actions that involved 45 labeling changes and 44 distinct products, including 1 product for which exclusivity was granted but no information was added to the label.

To structure its assessments, the committee devised a form that included both descriptive items (e.g., characteristics of requested studies, pediatric subgroups for which PREA studies were waived, and types of pediatric information added to product labels) and subjective assessments (e.g., appropriateness of permitting extrapolation for a pediatric age group, value of information generated by requested or required pediatric studies, and ethical status of a placebo-controlled clinical trial). The form required revisions as the specific circumstances identified in different assessments revealed the need for changes.

The committee began requesting redacted documents in early March 2011. The documents included written requests (and amendments); approval letters; and clinical, clinical pharmacology, and statistical reviews. For some products for which labeling changes were made in the late 1990s, the review documents were already posted at Drugs@FDA and thus did not need to be requested.

The committee supplemented the sample of written requests with additional requests in three areas: migraine, pediatric hypertension, and gastroesophageal reflux disease. It also reviewed requests, reviews, and other documents for many additional products or labeling changes as it investigated particular issues (e.g., neonatal studies). As described in Chapter 8, the committee examined a substantial number of documents for biologics as part of its work to identify biologics not evaluated in studies with children. In addition, it reviewed some FDA actions taken after December 31, 2010, to learn more about current practices (e.g., in waiving studies required under PREA).

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INSTITUTE OF MEDICINE
COMMITTEE ON PEDIATRIC STUDIES CONDUCTED UNDER BPCA AND PREA
MEETING 1: DECEMBER 17, 2010
Keck Building, 500 Fifth Street NW, Washington, DC
AGENDA: OPEN SESSION

9:30–Noon OPEN SESSION I
Introductions and chair's statement

U.S. Food and Drug Administration presentations

Overview and impact of the pediatric legislation (since 1997)
Dianne Murphy, M.D., Office of Pediatric Therapeutics

Elements of FDAAA 2007 and their implementation within CDER
Lisa Mathis, M.D., Center for Drug Evaluation and Research

Elements of FDAAA 2007 and their implementation within CBER and comments on IOM Tasks 5, 6, and 7
Jennifer Ross, Ph.D., Center for Biologics Evaluation and Research

Overview of the IOM task order, including data available
Robert "Skip" Nelson, M.D., Ph.D., Office of Pediatric Therapeutics

Comments on specific topics for IOM assessment
Drug labeling (IOM Tasks 1 and 2)
Dianne Murphy, M.D., Office of Pediatric Therapeutics

Extrapolation (IOM Task 3)
Julia Dunne, M.D., Office of Pediatric Therapeutics

Ethics, neonates, alternate endpoints (IOM Task 3)
Robert "Skip" Nelson, M.D., Ph.D., Office of Pediatric Therapeutics

Adverse events (IOM Task 4)
Judith Cope, M.D., M.P.H., Office of Pediatric Therapeutics

Questions from the committee

1:30–2:45 OPEN SESSION II
Welcome and introductions

Role of the National Institute of Child Health and Human Development in BPCA
Anne Zajicek, M.D., Pharm.D., Chief, Obstetric and Pediatric Pharmacology Branch, Center for Research for Mothers and Children

Information and process to support priority setting
Clifford Goodman, Ph.D., Vice President, The Lewin Group
Cynthia Schuster, M.P.P., The Lewin Group

Questions from the committee

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INSTITUTE OF MEDICINE
COMMITTEE ON PEDIATRIC STUDIES CONDUCTED UNDER BPCA AND PREA
MEETING 2: FEBRUARY 2, 2011
Keck Building, 500 Fifth Street NW, Washington, DC
AGENDA: OPEN SESSION

11:00–Noon
Thomas Boat, M.D., *Committee Chair*

Welcome and chair's statement

Lisa Mathis, M.D., Center for Drug Evaluation and Research
PREA waivers and deferrals and other issues
Julia Dunne, M.D., Office of Pediatric Therapeutics
European Medicines Agency (EMEA)

Questions from the committee

Noon Lunch

12:45–1:45
Continued FDA presentations and discussion

1:45–3:00
Daniel Frattarelli, M.D., F.A.A.P.
Chair of the American Academy of Pediatrics Committee on Drugs

Questions from the committee

3:00 Adjourn

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INSTITUTE OF MEDICINE
COMMITTEE ON PEDIATRIC STUDIES CONDUCTED UNDER BPCA AND PREA
MEETING 3: April 28, 2011
Keck Building, 500 Fifth Street NW, Washington, DC
AGENDA: OPEN SESSION

1:00 Public Session
Welcome and chair's statement
Thomas Boat, M.D., *Committee Chair*

Biotechnology Industry Organization
Ronald J. Portman, M.D.
Chair, Pediatric Drug Development Committee
Group Director, Pediatric Programs/CV/Metabolics
Bristol-Myers Squibb

Pharmaceutical Research and Manufacturers Association
Samuel D. Maldonado, M.D., M.P.H.
Vice-President and Head
Pediatric Drug Development Center of Excellence
Johnson & Johnson PRD

American Academy of Child and Adolescent Psychiatry (AACAP)
Adelaide Robb, M.D.
Chair, AACAP Pediatric Psychopharmacology Initiative
Director of Psychiatric Clinical Trials
Children's National Medical Center, Washington, DC

Pediatric Rheumatology Collaborative Study Group
Daniel J. Lovell, M.D., M.P.H.
Chair, Pediatric Rheumatology Collaborative Study Group
Professor of Pediatrics and Associate Director, Division of Rheumatology
Children's Hospital Medical Center, Cincinnati.

Perspectives from Clinicians and Parents Caring for Children with HIV Infection
Natella Y. Rakhmanina, M.D.
Associate Professor of Pediatrics, George Washington University
Director, Special Immunology Pediatric HIV Program
Children's National Medical Center, Washington, DC

Questions from the committee

3:00 Adjourn

Written statements submitted for this meeting:
Childhood Arthritis and Rheumatology Research Alliance (CARRA)
Friends of CARRA

B
Dissemination of Information from Pediatric Studies Conducted Under BPCA and PREA

P. Brian Smith and Matthew M. Laughon[*]

When the Food and Drug Administration (FDA) approves a sponsor's application to market a new product or approves a new use or formulation of an existing product, it also arrives at an agreement with the sponsor about the product's labeling. That label contains prescribing information for clinicians, including information about the approved uses and dosing (including uses, if any, for pediatric populations), pharmacology, safety, and supporting studies. However, the drug label frequently contains little pediatric prescribing information.

The lack of pediatric clinical trials evaluating drug dosing, safety, and efficacy is due in part to the specific challenges in conducting studies with children and, in part, the economic decisions by pharmaceutical sponsors. For most of the 20th century and with the exception of vaccines, most drug development was focused on adults, with perhaps one-quarter of drugs marketed in the United States labeled for pediatric use by the 1990s.[1] The FDA Modernization Act in 1997 and the Best Pharmaceuticals for Children Act (BPCA) in 2002 were designed to address this knowledge gap by providing incentives to pharmaceutical sponsors to study on-patent medications and a mechanism to encourage studies of off-patent medications in children. The Pediatric Rule and the Pediatric Research Equity Act (PREA) allowed FDA to require pharmaceutical sponsors to submit pediatric studies for products that might have substantial use by the pediatric population even when the drug manufacturer was seeking approval only for an adult indication. Since 1998, FDA has approved almost 400 pediatric-specific labeling changes.[2]

This paper examines what is known about how labeling information, including information about important changes in pediatric labeling, reaches physicians. It describes intermediary resources that include, to various degrees, information from the FDA label providing guidance on prescribing medications for children.

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PEDIATRIC USE AND PEDIATRIC LABELING

Many medications used by children are not specifically approved by FDA for such use. Often, information on pediatric use of a product is limited to a statement in the label that safety and efficacy in children have not been established. In other instances, the labeling includes brief information from pharmacokinetic (PK) studies as well as short descriptions of studies that did not demonstrate efficacy. Although most information comes from sponsor-supported studies, FDA occasionally seeks labeling changes after analyzing adverse event reports.[3]

In addition, safety reviews and recommendations by FDA's Pediatric Advisory Committee (PAC) have been available on FDA's website since 2002.[4,5] Safety information for the PAC is obtained from FDA's voluntary electronic Adverse Event Reporting System (AERS) available to physicians, pharmacists, patients, and parents. BPCA requires the FDA to report to the PAC safety concerns identified in AERS in the 1-year period following the granting of exclusivity. The PAC is able to recommend additional labeling changes, MedGuide production, or continued close surveillance.[6] MedGuides are FDA-approved patient information necessary for a patient's safe and effective use of prescription drugs that pose a serious public health concern. They are given to patients with each prescription. The FDA also provides, on its website, a list of all labeling changes that have occurred under BPCA and PREA with links to the product label.[2] AERS is limited, as it relies on voluntary reports, and because children represent a small percentage of the population receiving drugs for which adverse events are reported to the FDA, pediatric adverse events can get lost among the larger number of reports submitted for adults.

Off-label prescribing is a common cause of drug-related adverse events in children.[7] Improper dosing in children leads to higher rates of treatment failures, adverse events, mortality, and long-term morbidities.[8,9] Data on drug safety, PKs, pharmacodynamics (PDs), and efficacy for infants are even more limited than data for older children.[10–12]

Unfortunately, the relationship between drug action and drug exposure in children cannot be completely understood by extrapolating information obtained from studies in adults. Drug clearance is highly variable in children, particularly infants, because processes responsible for drug biotransformation and elimination are under active development. Dosing requirements for children are often substantially different from those for adults, and significant safety discrepancies have been identified[6,13,14] (Table B-1).For example, the requirement for fluconazole dosing for the treatment of invasive candidiasis in term and preterm infants is two times higher than that for adults (12 versus 6 mg/kg/day),[1□] and micafungin dosing requirements for infants are five times higher than those for adults (10 versus 2 mg/kg/day).□□□□□ For these drugs, simple allometric scaling applied in an effort to predict drug clearance across the continuum of development□□ would have limited accuracy due to true maturational differences in the pathways responsible for drug clearance.

TABLE B-1 Infant Dosing Compared with Adult Dosing of Commonly Used Antimicrobials for Bloodstream Infections

Drug	Preferred Adult Dose[a] (mg/kg/day)	Pediatric or Infant Dose (mg/kg/day)	PK Data Available for Infants Born <28 Weeks Gestation
Ampicillin[15]	150–200	150–200	None
Ciprofloxacin[16]	17	30	None
Daptomycin[17]	4–6	12	None
Metronidazole[18]	30	7.5–15	Limited (>7 days of life)
Fluconazole[19]	3–6	12	Yes
Micafungin[20,21,22]	2	10	Yes

[a] Calculated by dividing the recommended adult dose by 70 kg.

Although legislative efforts have resulted in a large number of pediatric-specific labeling changes, several limitations to these legislative efforts exist. Pharmaceutical sponsors are not obligated to respond to FDA's request for studies, and FDA can require studies only for the indication proposed in a sponsor's application. Few labeling changes have included infant-specific information. Infants and premature infants represented only 0.2 and 0.01 percent, respectively, of all children studied in trials submitted to FDA through the pediatric exclusivity program from 1998 to 2005.[2]

Notwithstanding the benefits of the FDA process for approving drugs and authorizing information in the product's labeling, the question about whether and how this information reaches physicians and how it influences clinical practice remains. The rest of this paper considers the first issue: dissemination of information about labeling changes.

FDA DISSEMINATION OF INFORMATION ABOUT LABELING CHANGES

FDA uses several strategies to disseminate information about labeling changes in general. At Drugs@FDA, FDA usually posts at least the letter approving a change and the revised label. For new drugs or new indications, FDA may post other information, including reviews of the information supporting the changes. For the subset of biologics (mainly blood products and vaccines) that are reviewed and approved by FDA's Center for Biologics Evaluation and Research, FDA posts information on labeling changes by year. To those who sign up, FDA offers email updates on a variety of topics. These include notices of new drug or biologic approvals, new safety warnings, and drug shortages.[26]

To disseminate information about labeling changes related to pediatric use, FDA also uses formal mechanisms authorized by Congress and cooperates with established sources that physicians who care for children consult for pediatric prescribing guidance. With the reauthorization of BPCA and PREA in the FDA Amendments Act (FDAAA),[27] Congress provided for greater public access to information generated from pediatric trials. For labeling changes approved after its date of enactment, FDAAA authorized the FDA to

provide public access to full medical, statistical, and pharmacological reviews of studies performed in response to FDA requests or requirements.

The FDA provides outreach directly to pediatric providers and researchers and to intermediaries who distribute pediatric prescribing information. For example, FDA provides a monthly column for the American Academy of Pediatrics (AAP) *Update of the American Academy of Pediatrics* on new dosing, safety, and efficacy findings. The FDA has also published a number of articles focusing on findings from pediatric trials stimulated by BPCA and PREA.[6,13,14,28–32] The FDA's Office of Pediatric Therapeutics has made efforts to work directly with the editors of *The Harriet Lane Handbook*, commonly used by pediatricians, to update dosing information.

New Meropenem Dosing as Proof of Concept of Identifying Sources of Disseminating Prescribing Information

As an illustration of how the FDA might address efficient and rapid dissemination of labeling changes, we present our experience with a meropenem trial completed under the BPCA off-patent mechanism.[33] This PK and safety trial for labeling was performed with 200 critically ill infants. The goal was to establish dosing guidelines for infants <91 days of age. To describe current use and dosing of meropenem in young infants by neonatal care providers and to identify preferred sources of current and new dosing information, we performed a web-based survey of neonatologists and neonatal nurse practitioners employed by the Pediatrix Medical Group, Inc., in 278 neonatal intensive care units.[34] Questions described clinical situations in subgroups of infants according to gestational age where meropenem might be used as the preferred antimicrobial and asked for proper dosing amount/frequency and sources of dosing information. We obtained complete responses from 116 providers. The majority (66 percent) had used meropenem, although meropenem does not have a labeled indication for premature infants. Among providers who used meropenem, 74 percent used a total daily dose of 40 mg/kg for the treatment of sepsis (dosing according to Neofax,[35] an online and print formulary for preterm and term infants), 4 percent used a lower dose, 7 percent used a higher dose, and 16 percent did not respond. For the treatment of meningitis, meropenem was dosed by 61 percent of providers at a total daily dose of 120 mg/kg (Neofax[35] dosing), 28 percent used a lower dose, 1 percent used a higher dose, and 10 percent did not respond. Neofax was the preferred source of new dosing information (80 percent), followed by pediatric infectious disease specialists, journals, and the hospital formulary (Figure B-1). Thus, the highest penetration of a new dose would be to target Neofax, followed by infectious disease specialists. Although the sample size is relatively small, this type of information is critical to target providers who will be prescribing medications.

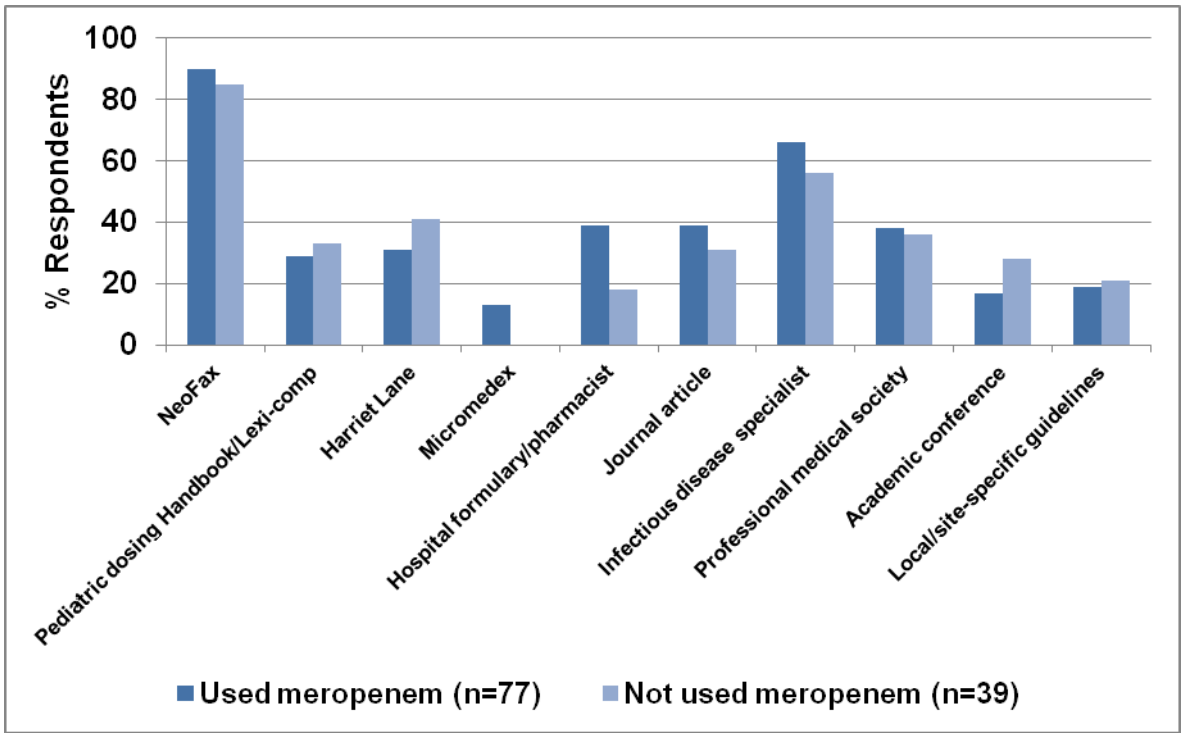

FIGURE B-1 Preferred sources of new dosing information.
SOURCE: Authors' survey of neonatologists and neonatal nurse practitioners employed by the Pediatrix Medical Group, Inc., in 278 neonatal intensive care units.

SOURCES OF PRESCRIBING INFORMATION USED BY PHYSICIANS TREATING CHILDREN AND ADOLESCENTS

Clinicians have available a large number of sources that offer prescribing information (Table B-2). They range from local pharmacies to professional societies and from government agencies to publicly traded companies.

TABLE B-2 Sources for Prescribing Information for Clinicians

Intermediary Resource	Publisher(s), Website	Advantages	Disadvantages
The Harriet Lane Handbook[36-38]	Johns Hopkins Hospital, Elsevier	Uses FDA label as source	Online version through mdconsult.com
Neofax	Thomson Reuters, http://www.skyscape.com/neofax/	Uses FDA label as source	Limited to infants
Epocrates[38]	Epocrates, www.epocrates.com	Uses FDA label as source, smart phone applications	Advertising might introduce bias
Lexi-Comp[38,39]	Lexi-Comp, www.lexi.com	Uses FDA label as source	
Micromedex	Thomson Reuters, www.micromedex.com		Directed toward hospital formularies
Physicians' Desk Reference[38,39]	PDR Network, www.pdr.net	Uses FDA label as source	
Red Book	American Academy of Pediatrics, www.aap.org	Free to AAP members	
Nelson's Pocket Book of Pediatric Antimicrobial Therapy[40]	American Academy of Pediatrics, www.aap.org	Free to AAP members	
Tarascon Pharmacopoeia[41]	Tarascon Publishing, www.tarascon.com		Limited pediatric data
Medscape/WebMD/eMedicine	www.medscape.com, www.emedicine.com, www.webmd.com	Free, Uses FDA label as source	Publicly traded company, advertising might introduce bias
MD Consult	Elsevier Publishing, www.mdconsult.com		Formulary outsourced to Gold Standard, Inc.
UpToDate	www.uptodate.com		Formulary linked to another source (Lexi-Comp)

Drug Facts and Comparisons	Wolters Kluwer Health, www.factsandcomparison.com	Uses FDA label as source	Used mostly by pharmacists
eMPR	Haymarket Media, www.empr.com	Update monthly	Advertising on website
AAP News[37]	American Academy of Pediatrics, www.aap.org	Unbiased	
Scientific literature[38]	Medline, CINAHL (Cumulative Index to Nursing and Allied Health Literature), Cochrane database, etc.	Abstracts usually free	Fully published article might require subscription, findings difficult to interpret
Pharmacy consultation[38]	NA[a]	Fast	Bias
Experience[38]	NA	Fast, efficient	Bias
Local pharmacy computer physician order entry pharmacy systems (e.g., Sunrise Clinical Manager[38])	NA	Fast	Uncertain how dosing information is derived
Subspecialist guidelines (e.g., pediatric infectious disease, pediatric gastroenterology)	http://www.guideline.gov/, other subspecialty sites		Bias
Drug label[42]	http://dailymed.nlm.nih.gov http://www.nlm.nih.gov/medlineplus/druginfo/meds/a606016.html http://www.accessdata.fda.gov/scripts/cder/drugsatfda/ http://www.fda.gov/BiologicsBloodVaccines/DevelopmentApprovalProcess/BiologicalApprovalsbyYear/default.htm	Free	Difficult to understand

[a] NA = not applicable.

Informal communication suggests that clinicians rarely, if ever, consult one available resource: the FDA-authorized drug label. To investigate further, we surveyed 30 pediatric residents and 10 general pediatric attending physicians at the University of North Carolina (UNC) and at Duke University Medical Center about whether they had consulted a drug label for pediatric dosing guidance. None of the 40 clinicians reported that they had read an FDA label or used the FDA label to obtain prescribing information. Most of the respondents reported using *The Harriet Lane Handbook*. Our informal survey is biased toward inpatient hospital providers. Similarly, in a published survey of 313 practitioners, there were no reports of the use of the drug's FDA label to guide pediatric dosing.[38] Some elements of the drug label are more often recognized than the sections on dosing. For example, FDA black box warnings have a relatively high penetration to outpatient providers (33 to 72 percent), although this may differ by specialty.[42–44] Many of the most commonly used medications in pediatrics have little to no pediatric-specific information.[39,45]

Cost of intermediary resources is an important issue. To keep knowledge up to date, most online sources require a subscription (e.g., UptoDate and MD Consult) and many print editions require purchase of a new book each year (e.g., *The Harriet Lane Handbook*). The sponsorship and funding of the resources in Table B-2 are opaque. Intermediary resources range from nonprofit professional groups (e.g., AAP) to publicly traded companies. Some sources, particularly those online (e.g., WebMD), are accompanied by drug advertising, and some are provided by pharmaceutical companies to residents (e.g., UNC residents receive free copies of *The Harriet Lane Handbook* from a pharmaceutical company). Researchers have found associations with higher prescribing frequency, higher costs, or lower prescribing quality when prescribers are provided with information from pharmaceutical companies, but no evidence of improved prescribing practice is available.[46] Ideally, the most commonly used sources of prescribing information would have unbiased information free from industry financial influence. To address this issue fully is beyond the scope of this paper. Concerns have also been expressed about industry influence on the content of professional society guidelines and continuing medical education offerings.[47]

Many of the dosing resources use the FDA label as a source of prescribing information. Most also have dosing recommendations for off-label use of medications for pediatrics. For example, Neofax has a recommended dose of intravenous immunoglobulin for severe hyperbilirubinemia due to Rh or ABO blood group incompatibility, an indication not approved by FDA for any approved intravenous immunoglobulin product.[35] Resources may rely on expert opinion or review of the medical literature for these indications. It is unclear how experts are chosen, although some are noted to be on the editorial boards of some sources.

Medscape/WebMD/eMedicine is a website covering a variety of health topics, including medications. This website has a section on the FDA, and it should be noted that the FDA and WebMD have a partnership to promote public health.[48] Certain articles on WebMD are under editorial control of the FDA and are noted as such.[48] The sections on WebMD that review pediatric medications refer to the FDA label and use expert opinion

and scientific literature for dosing recommendations. The date of the most recent update is noted on each webpage.

Some intermediary resources are directed specifically toward pediatric providers. The two most commonly used are *The Harriet Lane Handbook*[36] for pediatricians and Neofax for providers working in the neonatal intensive care unit. *The Harriet Lane Handbook* and Neofax use the FDA labels as a guideline and periodically update (usually every 1 to 2 years) the information provided in the book. The *Red Book*, an AAP publication that reviews infectious diseases and antimicrobial drugs, is available online and in print and directs users to the FDA website for the product label for antimicrobial agents and related therapy. In addition, Appendix II of the *Red Book* is devoted to the FDA licensure dates of selected vaccines in the United States. The *Red Book* also has a section on MedWatch. The *Red Book* is updated every 3 years, most recently in 2009. AAP also publishes *Nelson's Pocket Book of Pediatric Antimicrobial Therapy*, which is updated yearly.[40] Both of these resources are limited to antimicrobial therapy.

Other intermediary resources provide both adult and pediatric dosing. Online editions of Lexi-Comp,[49] Micromedex,[50] the *Physicians' Desk Reference*,[51] and the *Tarascon Pharmacopoeia*[41] update the information in the FDA label more frequently, approximately every 6 months. The print versions of Lexi-Comp, the *Physicians' Desk Reference*, Micromedex, and the *Tarascon Pharmacopoeia* are updated yearly. *Drug Facts and Comparisons*[52] has online and bound versions and includes appendixes on FDA New Drug Classification and Pregnancy Categories. *Drug Facts and Comparisons* is used primarily by pharmacists and hospital pharmacy and therapeutic committees.

Epocrates, MD Consult, and UpToDate are online-only resources with adult and pediatric pharmacological information. Epocrates is focused primarily on drug information and has a web-based online version. In addition, applications for each of the major mobile operating systems (e.g., iPhone, BlackBerry, Android, and Windows Mobile) are available.

Epocrates uses the FDA drug label, FDA drug safety alerts, and the primary medical literature for dosing recommendations and is updated once per week. MD Consult and UpToDate are primarily focused on medical diagnoses and treatment. However, both have some dosing information. MD Consult uses the FDA label and medical literature to update dosing guidelines for pediatric therapeutics and lists the most recent update on each webpage for the drug. UpToDate simply refers to Lexi-Comp directly. eMPR (www.empr.com) and *Monthly Prescribing Reference* are an online resource and a monthly periodical, respectively, with updated information on dosing. *Monthly Prescribing Reference* also has a pediatrics edition.

Medical centers and health systems may also provide prescribing resources as well as their own formularies. Both UNC and Duke have proprietary computer order entry systems with a local pediatric formulary on the back end that provides alerts to providers when an order includes a dosage outside the normally accepted range, as established from resources such as those described here combined with local pharmacy input. We found no information on how often these formularies are updated.

Although dosing guidelines are included in these intermediary resources, it remains unclear how or if clinicians follow the recommended dosing guidelines. For example, when clinicians prescribe antibiotics for preterm infants, the rate of compliance with recommendations ranges from 37 to 88 percent.[53] In addition, the extent to which the resources referenced in this paper influence practice depends on the content that is

available, the way in which information is presented, and other factors, including the economic and organizational context in which clinicians practice. In general, analyses demonstrate a wide variability in the effectiveness of clinical decision support tools.[54,55] For example, in a large national health plan, physicians who had access to a handheld electronic formulary (Epocrates) had similar patterns of prescribing nongeneric, nonformulary medications, compared to the prescribing patterns of those physicians without access to such a device.[54]

EXTENT TO WHICH LABELING CHANGES ARE REFLECTED IN RESOURCES

A systematic investigation of the extent to which information resources are updated in a timely and accurate way to reflect drug labeling changes was beyond the scope of this paper. However, we did investigate a few recent, significant pediatric labeling changes (Table B-3). Elements of some of these changes are reflected in the most recent editions of intermediary resources. However, some safety findings are not mentioned (e.g., those for topiramate and lamotrigine).[36] As noted earlier, information on off-label use is common. For example, dosing information is given for populations in which efficacy is not yet established (e.g., caspofungin) or efficacy was studied and not demonstrated (e.g., azithromycin).[35] Note that three of the labeling changes involved information based on pediatric studies with negative findings about safety or efficacy, or both. Neither *The Harriet Lane Handbook* nor Neofax routinely notes when dosing is recommended for off-label indications or age groups.[35,36,48,57] Neofax does, however, provide references for its dosing recommendations.[35]

TABLE B-3 Recent Pediatric Labeling Changes Identified by FDA and Comparison to Commonly Used Resources

Drug	Labeling Change	Date of Labeling Change	Information from:	
			The Harriet Lane Handbook	Neofax
Topiramate	Lack of efficacy for treatment of seizures for ages 1–24 months Growth retardation lab abnormalities for ages 1–24 months	12/22/2009	No dosing information for ages <2 years[36] New safety findings not mentioned[36]	No information provided[35]
Esomeprazole	Lack of efficacy for GERD[a] for ages <1 year	6/18/2009	No dosing information for ages <1 year[36] No reference to lack of efficacy for ages <1 year	No information provided[35]
Lamotrigine	Lack of efficacy for	5/8/2009	No dosing information	No information

	ages 1–24 months, seizures Associated with increased risk of infectious adverse reactions		for ages <2 years[36] *New safety findings not mentioned*[36]	provided[35]
Azithromycin	Efficacy for community-acquired pneumonia not established for ages <6 months Efficacy for sinusitis not established for pediatric population	10/8/2008	Dosing for otitis media and community-acquired pneumonia provided for ages ≥6 months[36] *Dosing for acute sinusitis provided for ages ≥6 months*[36]	*Dosing provided for infants*[35]
Caspofungin	Safety and efficacy not studied for ages <3 months	7/29/2008	*Dosing provided for ages <3 months*[36]	*Dosing provided for infants*[35]

[a] GERD = gastroesophageal reflux disease.

CONCLUSION

BPCA and PREA have addressed many of the knowledge gaps in pediatric therapeutics, but gaps remain. Many drugs used by children, especially infants, are used off-label for indications that are often not approved by FDA and for which dosing and safety information is not included in the FDA label.

Although FDA rigorously reviews the accuracy and completeness of drug labeling proposed by sponsors and revisions to proposed language are common, this paper suggests that the extent to which providers directly use labels is limited. Instead, clinicians who prescribe medication to children rely upon intermediary resources that come in various printed or online forms. FDA has many competing demands on its resources for investigation and dissemination, but possible shortcomings in the completeness and timeliness of drug information provided by intermediary resources are concerning.

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C
Biologics in Pediatrics

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Biologics have a long history of use as therapeutic agents in the United States (FDA, 2002). Vaccines, primarily derived from animal sources, were among the first biologics developed. The smallpox vaccine was introduced in 1800 (Barquet and Domingo, 1997), followed by other vaccines, such as the rabies and diphtheria vaccines (Junod, 2002). These vaccines were widely used but had little regulatory oversight. This changed in 1902 with the passage of the Biologics Control Act of 1902, which established regulations for vaccine production and licensing, following the deaths of 22 children in separate incidents involving contaminated diphtheria antitoxin and contaminated smallpox vaccine (Junod, 2002).

Since the time that these early biological products began to be regulated, advances in science and technology have allowed more purified and complex biologics, including those derived from human blood components or produced using recombinant technology[1] (Roque et al., 2004; Burnouf, 2011). Biologics are now used not only to prevent infectious conditions but also to treat a wide array of diseases, such as rheumatoid arthritis, cancers, and other immune-mediated conditions. Although some of these diseases are diagnosed in the pediatric population, research with these age groups is limited.

Since 1972, the Food and Drug Administration (FDA) has been responsible for the regulation of biologics. FDA licenses biological products under the Public Health Service Act licensing provisions and approves drugs under the federal Food, Drug, and Cosmetic (FDC) Act approval provisions. Under the FDC Act, certain old, relatively simple, biologically based products (e.g., insulin and human growth hormone) have long been regulated by the Center for Drug Evaluation and Research (CDER) through the New Drug Application process rather than through the Biologics License Application process of the Public Health Service Act (FDA, 2009c). In 2003, CDER also assumed responsibility for certain biologics. These are sometimes referred to as "therapeutic biologics," although responsibility for regulation of other therapeutic biologics, such as

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[1] Recombinant technology involves the combining of DNA sequences responsible for expression of specific proteins or the fusion of target regions of antibodies, antibody fragments, or proteins.

intravenous immune globulins, remained with the Center for Biologics Evaluation and Research (CBER). CDER-regulated biologics include monoclonal antibodies for in vivo use, cytokines, growth factors, enzymes, immunomodulators, thrombolytics, certain therapeutic proteins, and nonvaccine immunotherapies (FDA,2009d, 2010). Regulation of allergenics, blood and blood components (including recombinant proteins of blood components), gene therapy products, certain human cellular and tissue-based products (including stem cells and tissues for implantation or transplantation), vaccines, and nonhuman cells or tissues for transplantation remains under the authority of CBER (FDA, 2009a). This paper focuses on the biologics regulated by CDER and the CBER-regulated biologics that are derived from blood and blood components, with the exception of vaccines.

DEFINITION AND REGULATION OF BIOLOGICS

Generally described, biologics are "isolated from a variety of natural sources—human, animal, or microorganism—and may be produced by biotechnology methods and other cutting-edge technologies" (FDA, 2009e, unpaged). The regulatory definition provided in the Public Health Service Act (as amended in 2010) states that a biologic is "a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, protein (except any chemically synthesized polypeptide), or analogous product, or arsphenamine or derivative of arsphenamine (or any other trivalent organic arsenic compound) applicable to the prevention, treatment, or cure of a disease or condition of human beings" (42 USC 262(i)).

Biologics differ from conventional drugs in complexity and source. Unlike small-molecule drugs, which are produced by chemical reactions and have a known structure, biologics can be derived from human, microbiological, or animal sources and have complex structures consisting of amino acids, sugars, and nucleic acids (Figure C-1 shows an approximation of the difference in scale and complexity). Because of their higher complexity, stability is usually a greater issue with biologics than drugs (FDA, 2009e).

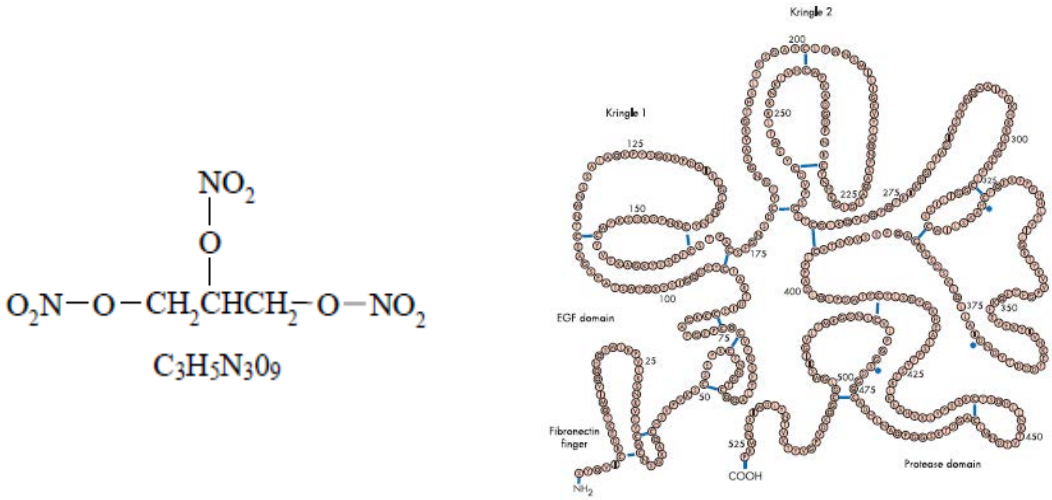

FIGURE C-1 Structures of nitroglycerin ($C_3H_5N_3O_9$), a conventional drug, and alteplase, a recombinant form of human tissue plasminogen activator.
NOTE: EGF = epidermal growth factor.
SOURCE: For alteplase, reproduced from *Heart*, T. K. Nordt and C. Bode, v.89, 1338-1362, 2003 with permission from BMJ Publishing Group Ltd.

OVERVIEW OF CHARACTERISTICS OF SELECTED BIOLOGICS

Some biologics are derived from blood, primarily plasma proteins (Table C-1), or are produced via recombinant technology (Tables C-2 and C-3). Plasma, either recovered from blood or donated directly, undergoes a fractionation process, which was first developed in the 1940s, to isolate proteins that can be used therapeutically (Burnouf, 2007). Isolation of a different protein occurs at each step of the fractionation process. For example, the first precipitate of the process—cryoprecipitate—is a rich source of coagulation proteins or factors (e.g., factor VIII and fibrinogen). Later in the fractionation process, other proteins such as albumin and immunoglobulins are separated out of the plasma after exposure to different ethanol concentrations and pHs. The safety of plasma-derived proteins is increased through the use of various methods to reduce the risk of transmission of human immunodeficiency virus, hepatitis viruses, and other viruses. These methods include chromatography (ion-exchange, affinity, and size-exclusion chromatography), filtration, solvent-detergent treatment, pasteurization, and heat treatment.

TABLE C-1 Plasma-Derived Therapeutic Proteins

Plasma-Derived Protein	General Uses
Coagulation factors (single factors and prothrombin complex)	Treatment or prevention of bleeding in patients with factor deficiency
Fibrinogen	Control of acute bleeding in patients with congenital fibrinogen deficiency
von Willebrand factor	Treatment or prevention of bleeding in patients with

Plasma-Derived Protein	General Uses
	von Willebrand disease
Thrombin (human and bovine)	Achievement of hemostasis during surgery
Antithrombin	Treatment or prevention of thromboembolism in patients with antithrombin deficiency
α_1-Antitrypsin (α_1-protease inhibitor)	Replacement therapy for patients with congenital α_1-Antitrypsin deficiency and emphysema
C1-esterase inhibitor	Prevention of angioedema in patients with hereditary angioedema
Immunoglobulins	Treatment of primary immunodeficiency diseases and immune thrombocytopenic purpura
Albumin	Treatment of fluid resuscitation and shock

SOURCES: Burnouf, 2007; McEvoy, 2011.

Beginning in the early 1980s, advances in genetic engineering and cell expression systems allowed production of recombinant forms of some human plasma proteins and the development of new biologics with specific cellular targets (Burnouf, 2011). Recombinant therapeutics generally include monoclonal antibodies, fusion proteins, and recombinant versions of human proteins (e.g., recombinant-derived coagulation factors). In addition to the different methods of production, recombinant therapeutics can differ in action, with some blocking or preventing release of cytokines and others acting as replacement proteins for deficient endogenous human proteins (Grabenstein, 2011).

Monoclonal antibodies represent the largest class of recombinant-derived therapeutics (An, 2010). Monoclonal antibodies have structures similar to those of immunoglobulins but are modified by recombinant technology to have a high specificity and affinity for a particular target, such as cytokines, cell markers, or their receptors, to prevent subsequent effects or production of inflammatory mediators (Table C-2) (An, 2010; Burnouf, 2011; Grabenstein, 2011). In addition to monoclonal antibodies, fusion proteins bind to cytokines or receptor sites to block the effects or production of cytokines (Table C-2). Fusion proteins consist of a portion of a native protein (e.g., a cell surface receptor) fused to another molecule, often via a portion of human immunoglobulin (Lee and Ballow, 2010).

TABLE C-2 Therapeutic Monoclonal Antibodies and Fusion Proteins

Biologic	Target	Source[a]
	Monoclonal antibodies	
Abciximab (ReoPro)	Glycoprotein IIb/IIIa receptor	Chimeric
Adalimumab (Humira)	Human tumor necrosis factor	Human
Certolizumab (Cimzia)	alpha	Humanized
Golimumab (Simponi)		Humanized
Infliximab (Remicade)		Chimeric
Alemtuzumab (Campath)	CD52 surface antigen on B and T lymphocytes; most monocytes, macrophages, and natural killer cells; and some granulocytes	Humanized
Basiliximab (Simulect)	Interleukin-2 receptor (CD25	Humanized

Biologic	Target	Source[a]
Daclizumab (Zenapax)	surface antigen) on activated lymphocytes	Humanized
Bevacizumab (Avastin)	Human vascular endothelial	Humanized
Ranibizumab (Lucentis)	growth factor-A receptor	Humanized
Canakinumab (Ilaris)	Interleukin-1β	Humanized
Capromab (ProstaScint)	Prostate-specific membrane antigen	Murine
Cetuximab (Erbitux)	Human epidermal growth factor	Chimeric
Panitumumab (Vectibix)	receptor expressed on normal and tumor cells	Humanized
Denosumab (Prolia/Xgeva)	Human receptor activator for nuclear factor-kappa B ligand	Humanized
Eculizumab (Soliris)	Complement protein C5	Humanized
Ibritumomab tiuxetan (Zevalin)	CD20 surface antigen on B lymphocytes	Murine
Ofatumumab (Arzerra)		Humanized
Rituximab (Rituxan)		Chimeric
Tositumomab, iodine I 131 tositumomab (Bexxar)		Murine
Muronomab (Orthoclone OKT3)	CD3 surface antigen of T cells	Humanized
Natalizumab (Tysabri)	α4-Integrin on the surface of all leukocytes except neutrophils	Humanized
Omalizumab (Xolair)	Human immunoglobulin E	Humanized
Palivizumab (Synagis)	The A antigenic site of F protein of respiratory syncytial virus	Humanized
Tocilizumab (Actemra)	Interleukin-6 receptor	Humanized
Trastuzumab (Herceptin)	Human epithelial growth factor receptor-2protein	Humanized
Ustekinumab (Stelara)	p40 subunits of interleukin-12 and interleukin-23	Humanized

Fusion proteins

Biologic	Target
Abatacept (Orencia)	CD80 and CD86 surface antigens on T cells
Alefacept (Amevive)	CD2 surface antigens on T cells
Etanercept (Enbrel)	Human tumor necrosis factor
Rilonacept (Arcalyst)	Interleukin-1 receptor
Denileukin (Ontak)	Interleukin-2 receptor
Romiplostim (Nplate)	Thrombopoietin receptor

[a] Sources of fragments used for monoclonal antibody production include human and nonhuman species. A portion of chimeric monoclonal antibodies (25 percent) are murine derived, humanized monoclonal antibodies are 5 percent murine derived, and human monoclonal antibodies are fully human. Immunogenicity is decreased with more human monoclonal antibodies.

SOURCES: An, 2010, Lee and Ballow, 2010; Burnouf; Grabenstein, 2011, 2011; McEvoy, 2011;Wickersham, 2011.

Finally, recombinant versions of human plasma proteins, as well as enzymes, have been developed for treatment of disorders resulting from qualitative or quantitative

deficiencies of these substances. These products are listed in Table C-3 (Rohrbach and Clarke, 2007; Brooker, 2008; Wickersham, 2011).

TABLE C-3 Additional Therapeutic Recombinant Human Proteins

Biologic	Description
Agalsidase beta (Fabrazyme)	Recombinant human form of α-galactosidase
Alglucosidase alfa (Myozyme/Lumizyme)	Recombinant human lysosomal glucogen-specific enzyme (α-glucosidase)
Alteplase (Activase)	Recombinant human tissue-type plasminogen activator
Anakinra (Kineret)	Nonglycosylated interleukin-1 receptor antagonist
Antithrombin alfa (ATryn)	Recombinant human antithrombin III
Becaplerin (Regranex)	Recombinant human platelet-derived growth factor
Darbepoetin alfa (Aranesp)	Recombinant human erythropoietin (modified by the addition of two carbohydrate chains)
Drotrecogin alfa (Xigris)	Recombinant activated human protein C
Ecallantide (Kalbitor)	Recombinant human reversible inhibitor of plasma kallikrein
Epoetin (Epogen)	Recombinant human erythropoietin
Factor IX (Benefix)	Recombinant human coagulation factor IX
Factor VIIa (NovoSeven-RT)	Activated recombinant human coagulation factor VII
Factor VIII, B domain deleted (Xyntha)	Recombinant human coagulation factor VIII with deletion of the B domain
Factor VIII, full length (Recombinate, Helixate, Kogenate, Advate)	Recombinant human coagulation factor VIII (antihemophilic factor)
Idursulfase (Elaprase)	Recombinant human iduronate-2-sulfatase
Interferon alfacon-1 (Infergen)	Recombinant hybrid of human interferon alpha
Interferon gamma 1B (Actimmune)	Recombinant human interferon gamma
Interferon beta (Betaseron, beta-1b; Avonex, Rebif, beta-1a)	Recombinant human interferon beta
Laronidase (Aldurazyme)	Recombinant human lysosomal glucogen-specific enzyme (L-iduronidase)
Naglazyme (Galsulfase)	Recombinant human lysosomal enzyme (*N*-acetylgalactosamine 4-sulfatase)
Oprelvekin (Neumega)	Recombinant human interleukin-11 (thrombopoietic growth factor)
Palifermin (Kepivance)	Recombinant analog of human keratinocyte growth factor
Pegfilgrastim (Neulasta)	Covalent conjugate of filgrastim and monomethoxypolyethylene glycol
Peginterferon alfa (Pegasys, alfa-2b; PEG-Intron, alfa-2b)	Recombinant human interferon alpha covalently bound to polyethylene glycol monomethoxy ether
Pegloticase (Krystexxa)	Pegylated recombinant human uric acid- specific enzyme
Rasburicase (Elitek)	Recombinant human of urate oxidase
Reteplase (Retavase)	Recombinant human tissue-type plasminogen activator

Biologic	Description
Tenectaplase (TNKase)	Recombinant human tissue-type plasminogen activator
Thrombin alfa (Recothrom)	Recombinant human thrombin

SOURCES: Burnouf, 2011; McEvoy, 2011; Wickersham, 2011.

The biologics described in Tables C-1 to C-3 are used for the treatment of a wide array of diseases and disorders (An, 2010; Burnouf, 2011). Because of their mechanisms of action, many of the monoclonal antibodies and fusion proteins are used for treatment of immune-mediated diseases, such as rheumatoid arthritis, Crohn's disease, multiple sclerosis, cancers, and psoriasis. Most are classified as antineoplastics, disease-modifying antirheumatic drugs, biologic response modifiers, or immunosuppressive agents (McEvoy, 2011). The activities of recombinant-based versions of human plasma proteins (e.g., epoetin, pegfilgrastim, antihemophilic factor, palifermin, and drotrecogin alfa) and enzymes (e.g., rasburicase, laronidase, naglazyme, and alglucosidase alfa) as well as plasma-derived proteins (e.g., immunoglobulins, albumin, von Willebrand factor, and C1-esterase) generally mimic the activity of the endogenous protein or enzyme to achieve a therapeutic effect.

CLINICAL PHARMACOLOGY OF BIOLOGICS

Well-established pharmacokinetic data for many drugs and biologics for the pediatric population are lacking. FDA has recognized the paucity of pediatric pharmacokinetic data and in response published draft guidance for industry in 1998 (FDA, 1998). The focus of the guidance was to elaborate on the pharmacokinetic information needed to determine appropriate medication doses in the pediatric population across all age groups, from neonates to adolescents. This determination is of particular concern in pediatrics because of growth and developmental changes that influence the absorption, distribution, metabolism, and excretion of drugs and biologics. Within the guidance, FDA recommended that pediatric pharmacokinetic studies evaluate how dosage regimens should be adjusted to attain "approximately the same level of systemic exposure that is safe and effective in adults" (FDA, 1998, p. 4).

If pediatric pharmacokinetic data are lacking for traditional drugs, these data are even scarcer for biologics, including monoclonal antibodies, although published data continue to expand (Dirks and Meibohm, 2010; Keizer et al., 2010). Monoclonal antibodies are immunoglobulins, which are used to treat a wide range of illnesses. Although there are five separate types of immunoglobulins in humans: immunoglobulin A (IgA), IgD, IgE, IgG, and IgM. An estimated 80 percent of all antibodies in humans are of the IgG family; all approved therapeutic monoclonal antibodies are of this family as well (Keizer et al., 2010).

The primary route of administration for approved monoclonal antibodies is intravenous (IV); however, some agents may be administered via the subcutaneous (SC) or intramuscular (IM) route (Keizer et al., 2010). Absorption via these secondary routes is facilitated by the lymphatic system, which often results in low to intermediate bioavailability. Peak concentrations in serum generally do not occur until a few days after

SC or IM administration because of slow absorption into the systemic circulation. Effective systemic therapy with monoclonal antibodies via the oral route is not currently possible because of their size, polarity, and the occurrence of gastrointestinal degradation. Monoclonal antibodies generally have low volumes of distribution primarily because of their large size and hydrophilic nature. Also, their bulky molecular size does not allow urinary excretion. Rather, monoclonal antibodies are metabolized to peptides and amino acids that are then either reused by the body or excreted by the kidney. The specific mechanisms of elimination of monoclonal antibodies are not well understood. In pediatric populations, specific pharmacokinetic parameters for monoclonal antibodies are not well studied.

The clearance of monoclonal antibodies from the body may be lengthened through a process called pegylation (i.e., the attachment of polyethylene glycol polymer chains to another molecule like a drug or therapeutic protein). Prolonging the half-life may allow reduced dosing or less frequent administration; however, this manipulation may also cause increased toxicities, such as a greater risk of allergic reactions. The formation of antibodies against monoclonal antibodies can have a significant impact on their efficacy in pediatric populations through effects on pharmacokinetics. The development of anti-monoclonal antibodies has been linked to a reduction in levels in serum and an increase in antibody clearance correlating to a reduced clinical response (Keizer et al., 2010).

For plasma-derived therapeutics, such as hemophilia factor concentrates and immune globulin intravenous (IGIV),[2] more specific, yet limited, pediatric pharmacokinetic data are available. In the pediatric population, both the clearance and volume of distribution of factor concentrates appear to increase with age and body weight (Bjorkman and Berntrop, 2001). In neonates administered IGIV for prevention of infection, the estimated elimination of IGIV was found to be quite prolonged: 16 to 36 days across various studies (Koleba and Ensom, 2006). In 2008, the FDA published a guidance regarding safety, efficacy, and pharmacokinetic studies to support marketing of IGIV as replacement therapy for primary humoral immunodeficiency (FDA, 2008). Within this guidance, the FDA recommended that "if possible and needed, the pharmacokinetic study of an IGIV product should be conducted across all pediatric age groups" (p. 10).

SAFETY CONCERNS IN PEDIATRIC POPULATIONS

Plasma-derived proteins such as coagulation factors and IGIV are commonly used to treat hemophilia and immune deficiency disorders in children, respectively. Historically, the major safety concern with these proteins was the risk of blood-borne infections; however, donor screening, improved testing methods (e.g., nucleic acid amplification), and viral inactivation procedures in the manufacturing process have made the potential for infection less of a concern (Tarantino et al., 2007; Radosevich and Burnouf, 2010). Today, there are different safety concerns with each of these products.

[2] Although immune globulin intravenous (IGIV) is the official name of these products, many clinicians continue to refer to these plasma-derived therapeutics as intravenous immune globulin (IVIG).

For pediatric patients with hemophilia, inhibitor development may be a serious roadblock to successful therapy. An inhibitor is a type of antibody, and in the case of hemophiliacs, these antibodies attach to coagulation factor VIII or factor IX and inhibit the ability of the factor to stop bleeding (DiMichele, 2008). As opposed to patients without inhibitors, hemophiliacs who develop inhibitors to factor products experience orthopedic and life-threatening bleeding complications more frequently because of the difficulties with the treatment of such patients (DiMichele, 2008). In addition, these individuals experience more disability in their everyday activities (DiMichele, 2008).

A variety of potential safety concerns arise with the administration of IGIV, with infusion-related reactions (arising from the triggering of an inflammatory response by components within an IGIV preparation) of various severities being the most common (Duhem et al., 1994; Nydegger and Sturzenegger, 1999). These reactions are often mild, self-limiting, and more common in IGIV-naïve patients and generally occur within 30 to 60 minutes after the start of an infusion. This reaction may manifest itself clinically as a low-grade fever, chills, mild headache, myalgias, and backache. Anaphylactic reactions occur rarely (<5 percent of IGIV recipients) and are most commonly observed in patients with IgA deficiency. The use of products that contain large amounts of IgA should be avoided in these patients (Nydegger and Sturzenegger, 1999).

Other rare, but serious, adverse events that can occur with IGIV administration include renal failure, aseptic meningitis, hemolysis, transfusion-related acute lung injury, and thrombotic events. Renal failure most commonly occurs with the use of sucrose-containing IGIV products (Epstein and Zoon, 1999).

Long-term safety concerns for certain biologics—in particular, the chronic administration of human tumor necrosis factor (TNF) inhibitors such as adalimumab, etanercept, and infliximab—may be quite serious (Hashkes et al., 2010). These concerns, which are controversial, include the possible occurrence of malignancies; an increased risk of serious infections; and the development of autoimmune phenomena such as demyelinating disease, autoantibodies, uveitis, lupus-like syndrome, inflammatory bowel disease, and psoriasis. A search of FDA's Adverse Event Reporting System (through April 29, 2008) revealed 48 cases of malignancy among pediatric patients prescribed TNF inhibitors, primarily for inflammatory bowel disease (Diak et al., 2010). Although the reported malignancy rates among children who received infliximab and etanercept were found to be higher than the background rates in the general pediatric population, a clear causal connection could not be established due to confounding factors such as concurrent immunosuppressant therapy and the potential risk of malignancy associated with underlying illnesses.

Administration of TNF inhibitors had been associated with an increase in granulomatous infections, particularly tuberculosis, prior to the widespread implementation of pretreatment screening and administration of appropriate prophylactic medications (Keane et al., 2001; Wallis et al., 2004; Hashkes et al., 2010). Reports of such infections in children administered these agents have subsequently decreased since 2000, with only a few case reports demonstrating development of tuberculosis (Myers et al., 2002; Armbrust et al., 2004) and histoplasmosis (Lee et al., 2002) being published.

Because of the complex effects of TNF in the immune system, inhibition may lead to autoimmune phenomena, including the development of autoimmune disorders for which TNF inhibitors are standard treatments, though a definitive association of

autoimmune disorders with TNF inhibitors has not been shown. Published case reports have documented the occurrence of a variety of these phenomena in children prescribed TNF inhibitors, including psoriasis (Peek et al., 2006), demyelination (Mohan et al., 2001), uveitis (Hashkes and Shajrawi, 2003), autoantibody development (Kanakoudi-Tsakalidou et al., 2008), diabetes mellitus (Bloom, 2000), systemic lupus erythematosus (Lepore et al., 2003; Bout-Tabaku et al., 2007), autoimmune hepatitis (Fathalla et al., 2008), and Crohn's disease (Ruemmele et al., 2004; Wiegering et al., 2010).

Infusion or injection-site reactions are common with administration of TNF inhibitors and other biologics such as interleukin-1 receptor antagonists (i.e., anakinra) and fusion proteins (Hashkes et al., 2010). Injection-site reactions (erythema, pruritus, pain, edema) occur frequently with the TNF inhibitors etanercept and adalimumab (28 to 39 percent) but do not often result in discontinuation of therapy. In contrast, infusion-related reactions with infliximab (fever, chills, dyspnea, urticaria, and hypotension, which may be due to anaphylaxis or the development of antibodies to infliximab) have been reported to result in cessation of therapy in approximately 20 percent of pediatric patients with juvenile idiopathic arthritis in a long-term prospective study (Gerloni et al., 2008).

BIOLOGICS AND DISEASES AFFECTING CHILDREN

Although pediatric diseases are often acute and self-limiting (e.g., otitis media, respiratory infections, and gastrointestinal illnesses), some children develop chronic health problems such as asthma, diabetes, cystic fibrosis, obesity, malnutrition, cerebral palsy, behavioral disorders such as attention deficit-hyperactivity disorder and autism, mental illnesses such as depression, and consequences of low birth weight and prematurity (i.e., retinopathy, chronic lung disease, and developmental delays) (Torpy et al., 2010).

For the majority of these conditions, biologics are not currently employed as treatment options. However, there are exceptions, including insulin—a product not regulated by FDA as a biologic but originally derived from animal sources and now through recombinant methods—for the treatment of diabetes and omalizumab (Xolair), a monoclonal antibody, approved for use as an adjunctive therapy in moderate to severe persistent asthma in patients 12 years of age and older (National Heart, Lung, and Blood Institute, 2007). Other biologics are being studied for the treatment of some of the conditions listed above, for example, forms of botulinum toxin for spasticity in cerebral palsy (see Appendix D).

The following sections review data on the use of biologics for the treatment of selected conditions in the pediatric population. The section on treatment of choice briefly reviews pediatric disorders in which a biological agent is the primary or preferred treatment option. The section on potential therapeutic options covers a variety of disease states for which biologics are either approved alternative agents or for which data are fairly limited. The goal of the latter section is not only to identify current pediatric biologic-related data in major branches of medicine (rheumatology, dermatology, gastroenterology, oncology, and endocrinology) but also to discuss gaps in our current clinical knowledge and use of these agents in pediatrics.

Biologics as the Treatment of Choice for Certain Disorders

Some diseases, although not widespread among children, commonly employ biologics, particularly plasma-derived or recombinant products, as treatment options. Examples of these diseases include hemophilia/bleeding disorders, immune deficiency syndromes, Kawasaki disease, and immune thrombocytopenic purpura (ITP).

Hemophilia

Hemophilia is a chromosome X-linked congenital bleeding disorder (World Federation of Hemophilia Guidelines, 2005). Globally, the number of affected individuals is approximately 400,000. In the United States, the Centers for Disease Control and Prevention (CDC) reports that hemophilia occurs in about 1 in 5,000 male births and that about 400 infants are born with the condition annually. Currently, the CDC estimates that about 20,000 people in the United States have hemophilia (Soucie et al., 1998).

The disease is caused by a deficiency in coagulation factors, specifically, factor VIII deficiency (hemophilia A) or factor IX deficiency (hemophilia B), with hemophilia A accounting for about 80 to 85 percent of all diagnoses (World Federation of Hemophilia Guidelines, 2005). Prevention and treatment of bleeding in individuals with hemophilia are accomplished through the administration of plasma-derived or recombinant products that supply these deficient factors. Although hemophilia qualifies as a rare disease under the Orphan Drug Act and many antihemophilic biologics have orphan drug designations and are exempt from the Pediatric Research Equity Act, all of the products that are listed in Appendix D are labeled for pediatric use for at least one indication.

The World Federation of Hemophilia guidelines state that two issues deserve special consideration when a choice regarding factor replacement therapy is made for patients with hemophilia: product purity and viral inactivation/elimination (World Federation of Hemophilia Guidelines, 2005). Although no classification of factor products based on purity is universally agreed upon, high-purity factor IX products are preferable for the treatment of hemophilia B because of a reduced risk of thromboembolic complications compared with the risk associated with the use of other plasma-derived products, such as prothrombin complex concentrates. The purity of the factor VIII product does not appear to enhance safety for patients with hemophilia A; therefore, this product characteristic does not affect factor VIII product selection.

With regard to viral inactivation/elimination, the World Federation of Hemophilia simply states that plasma quality and testing of the factor concentrate should definitely be considered but does not firmly recommend a particular coagulation factor product as being a safer option. In addition, the federation "does not express a preference for recombinant over plasma-derived concentrates and the eventual choice between these classes of product will be made according to local criteria" (World Federation of Hemophilia Guidelines, 2005, p. 31). This is in contrast to the United Kingdom Hemophilia Center Doctors' Organization (UKHCDO) guideline on the selection and use

of therapeutic products to treat hemophilia and other hereditary bleeding disorders (Keeling et al., 2008). The UKHCDO document specifically recommends recombinant factor VIII and factor IX as the treatments of choice for hemophilia A and B, respectively. This recommendation is due to a theoretical reduced risk of infectious agent transmission with recombinant products.

Primary Immune Deficiency Syndromes

Primary immune deficiency syndromes are inherited disorders that can result in an increased rate and severity of infection, immune dysregulation with autoimmune disease, and malignancy (Bonilla et al., 2005). More than 100 different genetic disorders that affect immune function have been identified, occurring in as many as 1 in 2,000 live births. For certain immune deficiencies, such as severe combined immunodeficiency or complement/phagocyte defects, bone marrow transplantation is the primary treatment option.

For other primary syndromes, such as common variable immunodeficiency, chromosome X-linked agammaglobulinemia, or autosomal recessive agammaglobulinemia, administration of IGIV or subcutaneous immunoglobulin is the treatment of choice. These products may also be used as adjunctive therapies in other situations (Bonilla et al., 2005; Roifman et al., 2008). A variety of IGIV products for treatment of primary immune deficiency syndrome are currently commercially available. Although they are often used interchangeably, the components of some IGIV products may be contraindicated in patients with certain medical conditions. For example, some IGIV formulations contain sucrose, which may contribute to the development or progression of renal insufficiency or failure (Siegel, 2010). In neonates, additional concerns exist regarding minimizing fluid volume and the pH and osmolarity of the IGIV solution. All of these factors must be taken into consideration when an appropriate IGIV product is chosen.

Kawasaki Disease

Kawasaki disease is an acute, self-limiting vasculitis of childhood that is most prevalent in Japan and among children of East Asian ancestry (Newburger et al., 2004). Approximately 4,250 Kawasaki disease-related hospitalizations occurred in the United States in 2000, with the median age at the time of diagnosis being 2 years. Symptoms of the disease include fever, bilateral nonexudative conjunctivitis, erythema of the lips and oral mucosa, changes in the extremities, rash, and cervical lymphadenopathy. An estimated 15 to 25 percent of untreated children develop coronary artery aneurysms or ectasia, which may subsequently lead to ischemic heart disease or sudden death.

The American Academy of Pediatrics (AAP) and American Heart Association (AHA) recommend IGIV, in combination with aspirin, as the first-line treatment for children with Kawasaki disease (Newburger et al., 2004). The AAP/AHA statement on management of Kawasaki disease specifically states that “the results of clinical studies comparing the efficacy of immune globulin products have conflicted, with most studies

failing to find a significant difference between brands" (Newburger et al., 2004, p. 1720). The choice of IGIV product basically comes down to patient and product characteristics, similar to IGIV selection for primary immune deficiency syndrome.

Immune Thrombocytopenic Purpura

Immune Thrombocytopenic Purpura (ITP) is an autoimmune disorder characterized by a low platelet count. The disease is often classified on the basis of the age of the patient (child versus adult), illness duration (acute versus chronic), and underlying disorder (primary versus secondary) (Blanchette and Bolton-Maggs, 2010). In children, the diagnosis of ITP is often one of exclusion (Provan et al., 2010). With acute ITP (low platelet counts for ages <6 months), children present with sudden onset of bruising or petechial rash, often preceded by an acute infectious illness such as an upper respiratory infection (Blanchette and Bolton-Maggs, 2010). Approximately 20 to 25 percent of these children will continue on to chronic ITP (i.e., low platelet counts for longer than 6 months after the initial diagnosis). Clinically significant symptoms of ITP are not common but may include severe epistaxis, gastrointestinal bleeding, and intracerebral hemorrhage (Provan et al., 2010). A recent international consensus report on the management of primary ITP recommended plasma-derived therapeutics, IGIV, and IV anti-D immunoglobulin as first-line treatment options in children when therapy is warranted (Provan et al., 2010).

Potential Therapeutic Options for Other Selected Pediatric Disorders

Rheumatology: Juvenile Idiopathic Arthritis

Juvenile idiopathic arthritis (JIA) is defined by the International League of Associations for Rheumatology as "arthritis of unknown etiology that begins before the 16th birthday and persists for at least 6 weeks" (Petty et al., 2004, p. 390). JIA encompasses a group of heterogeneous arthritic conditions, including systemic arthritis, oligoarthritis, polyarthritis, psoriatic arthritis, enthesitis-related arthritis, and undifferentiated arthritis. In Europe and North America, the incidence of JIA is estimated to be approximately 10 to 19 cases per year for every 100,000 children (Gare, 1999). Globally, prevalence rates for juvenile arthritis vary widely, from 0.07 to 4.01 per 1,000 children, because of various factors, including differing case definitions and development of new diagnostic criteria (Manners and Bower, 2002).

Four biological agents have been approved by the FDA for treatment of moderate to severe JIA. These include

- Etanercept (Enbrel)—approved for polyarticular JIA in patients 2 years of age or older (Amgen, 2011)
- Adalimumab (Humira)—approved for treatment of polyarticular JIA in patients 4 years of age and older (Abbott Laboratories, 2011)

- Abatacept (Orencia)—approved for treatment of polyarticular JIA in patients 6 years of age and older as monotherapy or in combination with methotrexate (Bristol-Myers Squibb, 2009)
- Tocilizumab (Actemra)—approved for treatment of systemic JIA in patients 2 years of age and older (Genentech, 2011)

Etanercept was the initial biologic to receive approval for treatment of polyarticular JIA in children on the basis of results from a randomized, double-blind, multicenter study involving 69 patients (ages 4 to 17 years) (Lovell et al., 2000). The study design involved up to 3 months of open-label etanercept therapy, followed by a double-blind period where patients were randomly assigned to receive either etanercept or placebo for 4 months or until disease flare occurred. Response to therapy during the open-label period was defined as an improvement of 30 percent or greater in at least three of six disease activity indicators, with no greater than one indicator worsening by more than 30 percent. Of the 69 pediatric patients enrolled in the open-label phase, 51 (74 percent) achieved a response to etanercept therapy and were then randomized to receive etanercept or placebo during the double-blind period. Results from the double-blind phase revealed that significantly more patients administered placebo than those receiving etanercept withdrew because of a disease flare (81 versus 28 percent). In addition, etanercept therapy was associated with a significantly longer median time to disease flare (116 versus 28 days). No significant differences in the frequency of adverse effects were observed between etanercept and placebo. In a long-term follow-up of patients from the original trial who continued on open-label etanercept, the efficacy and safety of etanercept were maintained for up to 8 years (Lovell et al., 2008a). No cases of serious adverse events such as lupus, demyelinating disorders, malignancies, or lymphomas were reported; nine medically important infections were seen over this time period, translating to an exposure-adjusted rate of 0.03 events per patient-year.

The efficacy and safety of adalimumab for JIA were established through the results of a randomized, double-blind, stratified, placebo-controlled study enrolling 171 pediatric patients (ages 4 to 17 years) (Lovell et al., 2008b). The study design consisted of a 16-week open-label lead-in phase (during which patients were stratified according to methotrexate use and all received adalimumab therapy), followed by a 32-week double-blind withdrawal phase and then an open-label extension. After the lead-in phase, 133 patients fulfilling the American College of Rheumatology (ACR) Pediatric (Pedi) 30 response criteria were randomly assigned to receive either adalimumab or placebo for 32 weeks. The primary outcome measure was disease flare occurrence during the double-blind period in the group of patients not receiving methotrexate. Results revealed disease flares to be less common among patients receiving adalimumab regardless of concurrent methotrexate use (43 versus 71 percent in patients not receiving methotrexate and 37 versus 65 percent in patients administered methotrexate). The number of pediatric patients who had ACR Pedi 30, 50, 70, or 90 responses was significantly greater for those receiving adalimumab in combination with methotrexate than those receiving methotrexate therapy alone. The differences between patients who received adalimumab but not treated with methotrexate and those who received placebo were not significant. Response rates were sustained even after 104 weeks of open-label extension therapy, with 40 percent of children experiencing an ACR Pedi 100 response. Fourteen serious

adverse events were determined to be possibly related to adalimumab, including seven serious infections (e.g., bronchopneumonia, herpes simplex, pharyngitis, pneumonia, and herpes zoster).

Abatacept was found to be an effective and safe treatment for JIA in a double-blind, randomized, controlled, withdrawal, multicenter trial enrolling 190 pediatric patients (ages 6 to 17 years) with a similar design to the previous studies (Ruperto et al., 2008). After the lead-in phase, 122 children who achieved an ACR Pedi 30 response were randomly assigned to receive abatacept or placebo for 6 months or until a flare of arthritis occurred. Results revealed that arthritic flares occurred more frequently with placebo than abatacept therapy (53 versus 20 percent). In addition, the risk of disease flare during the double-blind period for patients administered abatacept was less than a third of that for controls. The frequency of adverse events was similar between the groups, with only two serious adverse events being reported, and both of these occurred in the placebo group.

Tocilizumab is the most recent biological agent to receive approval by the FDA for JIA and was approved specifically for the subset of patients with systemic JIA. This approval was based upon results from a double-blind, placebo-controlled trial enrolling 112 children ages 2 to 17 years with systemic JIA who had an inadequate response or who were unable to take nonsteroidal anti-inflammatory drugs and corticosteroids. Eighty-five percent of patients receiving tocilizumab but only 24 percent of patients receiving placebo experienced at least an ACR Pedi 30 response along with absence of fever in the preceding 7 days (Genentech, 2011). The most commonly reported serious infections included pneumonia, gastroenteritis, varicella, and otitis media. This trial was supported by a randomized withdrawal trial enrolling 56 children (ages 2 to 19 years) with disease refractory to conventional treatments (Yokota et al., 2008). Patients were randomly assigned to tocilizumab or placebo for 12 weeks or until withdrawal for rescue medication, following a 6-week open-label phase to determine responders. The primary outcome measure of the double-blind phase was an ACR Pedi 30 response and C-reactive protein concentrations of <15 mg/L. Results for the 43 patients in the double-blind phase revealed that significantly more patients receiving tocilizumab than patients receiving placebo met the primary endpoint (80 versus 17 percent). Continued efficacy of tocilizumab was noted through week 48 of the open-label extension phase. Gastroenteritis, bronchitis, and anaphylactoid reaction were among the serious adverse events reported in the study.

Beyond the approved agents, studies have been conducted with other biologics, including infliximab (Ruperto et al., 2007) and anakinra (Quartier et al., 2011). Ruperto and colleagues (2007) concluded that the combination of various doses of infliximab and methotrexate produced a rapid, durable response in children with polyarticular JIA at 1 year; however, the primary endpoint of the study (ACR Pedi 30 at week 14) did not reveal a significant difference between infliximab and placebo (Ruperto et al., 2007). Less positive results were also seen with anakinra therapy for systemic JIA, which has an extremely difficult to treat systemic inflammatory component compared with polyarticular JIA (Quartier et al., 2011). After 1 month of treatment, a significantly higher proportion of responders was found among those receiving anakinra therapy than those receiving placebo; however, a loss of response was seen with most patients over time.

In contrast to many other pediatric diseases, several biologics are approved for use by pediatric patients with JIA; however, various unanswered, challenging questions that can be addressed only through rigorous clinical trials remain. These issues include the following (Pain and McCann, 2009):

- Which biologic is most beneficial in which JIA subgroup?
- What is the benefit, if any, of changing biologics if a TNF inhibitor fails?
- What is the duration of biologic therapy for children with JIA? Would children benefit from gradual dose reduction or frequency of administration if they were on long-term therapy?
- Should the biologic with the most efficacy and safety data, etanercept, be used only for refractory disease, or should it be considered for use as an initial treatment?
- Since no head-to-head trials of biologics in patients with JIA have been conducted, should such a trial be completed?

Dermatology: Atopic Dermatitis

Atopic dermatitis is a chronic, relapsing, eczematous skin disease generally characterized by pruritus and inflammation (Saeki et al., 2009). It is one of the most common skin disorders among children, with a prevalence of 10 to 20 percent in the United States (Spergel, 2010). Most children appear to develop symptoms of the disease early in life (age <2 years). Historically, atopic dermatitis was thought to be a disease that spontaneously resolved; however, more recent studies have found that 50 percent of patients continue to have intermittent symptoms until 7 years of age and others will continue to manifest symptoms into adulthood. In addition, children with atopic dermatitis are more likely to be diagnosed with other atopic diseases such as asthma or allergic rhinitis.

Treatment of mild to moderate atopic dermatitis generally involves the use of emollients alone or in combination with other topical therapies (Bremmer et al., 2009; Saeki et al., 2009); however, severe, persistent disease often requires systemic treatments or phototherapy. No systemic agents, including biologics, have been approved for the treatment of atopic dermatitis in children. Many of the currently available systemic therapies for severe disease have potential toxicities and modest efficacy; therefore, biologics may be another option for children with severe atopic dermatitis, though none have been approved by the FDA as safe and effective treatments (Bremmer et al., 2009).

Clinical data about the use of biologics for treatment of atopic dermatitis are limited to case reports and small open-label pilot studies for both pediatric and adult populations (Buka et al., 2005; Jacobi et al., 2005; Krathen and Hsu, 2005; Lane et al., 2006; Vigo et al., 2006; Weinberg and Siegfried, 2006; Hassan et al., 2007; Siegfried, 2007; Takiguchi et al., 2007; Moul et al., 2008; Simon et al., 2008). In the pediatric-specific reports, results with biologic therapy (i.e., efalizumab, omalizumab, and etanercept) have varied (Buka et al., 2005; Vigo et al., 2006; Weinberg and Siegfried, 2006).

Dermatology: Psoriasis

Psoriasis is a common, chronic disease that predominantly affects the skin and joints; approximately 7.5 million people in the United States are affected (Menter et al., 2008; National Psoriasis Foundation, 2011). Many different types of psoriasis exist, including plaque (occurring in approximately 80 to 90 percent of people with psoriasis), inverse, erythrodermic, pustular, and guttate (Menter et al., 2008). The primary clinical manifestation of psoriasis is disfiguring, scaling, and erythematous skin plaques that may be painful or pruritic. Plaques may occur anywhere on the body but are most commonly seen on the elbows, knees, scalp, buttocks, and lower back. The disease can range in severity from mild to severe, with symptoms improving or worsening over time. An estimated 80 percent of individuals with psoriasis have mild to moderate disease. This form of the disease is often effectively managed with localized topical therapies. The remaining 20 percent have moderate to severe disease, which may often require the use of biologic therapy.

Although psoriasis can occur at any age, the disease is more common in individuals between 15 and 30 years of age and then later in life between the ages of 50 and 60 years (Levine and Gottlieb, 2009). Data on the incidence of psoriasis among children are limited; however, a recent population-based retrospective study found the overall age- and sex-adjusted annual incidence of pediatric psoriasis to be 40.8 per 100,000 (Tollefson et al., 2010). In addition, the incidence of psoriasis among children was found to increase significantly over time: 29.6 per 100,000 (1970 to 1974) to 62.7 per 100,000 (1995 to 1999). The most common type of psoriasis reported was plaque psoriasis (74.7 percent), followed by guttate psoriasis (14 percent). Although the exact incidence of moderate to severe psoriasis among the pediatric population is unknown, it has been reported that approximately 8 percent of pediatric patients with psoriasis require phototherapy or systemic medications (Sukhatme and Gottlieb, 2009). The onset of psoriasis in childhood does not always lead to persistence into adulthood and is not correlated with severity of disease in adult life.

In addition to the cutaneous manifestations, psoriasis has been associated with several nondermatological comorbidities, including arthritis, cardiovascular disease, diabetes, obesity, Crohn's disease, and depression (Sukhatme and Gottlieb, 2009; Marji et al., 2010). For pediatric patients with moderate to severe psoriasis, the emotional and psychological impact of this chronic disease cannot be overestimated. Currently, none of the available biologics is approved for use by children with moderate to severe psoriasis. In 2008, an FDA advisory panel voted to recommend approval of etanercept for treatment of moderate to severe plaque psoriasis in children and adolescents unresponsive to other therapies. However, the manufacturer (Amgen) declined to continue with the approval process.

The advisory panel recommendation was based only on data from a multicenter study involving 211 patients (ages 4 to 17 years) with moderate to severe plaque psoriasis (Paller et al., 2008). The study design included three phases: an initial 12-week randomized, double-blind, placebo-controlled treatment period, followed by a 24-week open-label treatment period and, finally, another 12-week randomized, double-blind, withdrawal-retreatment period. The primary endpoint was a composite of 75 percent or greater improvement from baseline in the psoriasis area and severity index (PASI 75) at

week 12. Results revealed that significantly more patients receiving etanercept than patients receiving placebo achieved PASI 75 (57 versus 11 percent; $p < 0.001$) at week 12. During the open-label treatment period, 62 percent of patients who were originally administered placebo and 69 percent who continued to receive etanercept from study initiation achieved PASI 75 at week 24. This level of response was maintained through week 36. During the final 12-week withdrawal-retreatment phase, response was lost in 29 (42 percent) of the 69 patients randomly assigned to placebo. These pediatric patients were then retreated with etanercept, with response rates being similar to those for patients initially treated with the biologic. Evaluation of safety concerns showed that the rates of infectious and noninfectious adverse events were similar between etanercept and placebo. Only a few serious adverse infectious events in patients on etanercept were noted: a 7-year-old with a history of asthma was treated with IV antibiotics for left basilar pneumonia, and a 9-year-old experienced concurrent serious episodes of gastroenteritis. No cancers, opportunistic infections, tuberculosis, or demyelination events were reported, though subjects were monitored for only 48 weeks.

The remaining published clinical data involving etanercept for the treatment of pediatric psoriasis are from single case reports or case series (Hawrot et al., 2006; Kress, 2006; Papoutsaki et al., 2006; Safa et al., 2007; Floristan et al., 2011). The outcomes of these reports have primarily been favorable, with improvement of severe disease and only minor adverse events being reported. Data are even more limited or nonexistent for other biologics. Currently, only two case reports of infliximab administration in pediatric patients with psoriasis have been published (Menter et al., 2004; Farnsworth et al., 2005). One of these reports details the successful use of infliximab following a failed treatment course of etanercept (Farnsworth et al., 2005).

Of the dermatologic conditions, no controlled trials involving biologic therapies for severe atopic dermatitis have been published. Published data primarily involve case reports with various outcomes with the biologic administered. More data are available for biologic administration for psoriasis; however, basic gaps in our understanding remain, including the place in therapy for biologics (i.e., should these agents be used only after other systemic treatments); appropriate dosing regimens; and long-term safety concerns, including the potential increased risk of lymphoma and other cancers in children and adolescents administered TNF inhibitors (FDA, 2009b).

Gastroenterology: Inflammatory Bowel Disease

Crohn's disease and ulcerative colitis, the two major types of inflammatory bowel diseases (IBDs), are both chronic conditions manifesting with exacerbation and remission of severe diarrhea, rectal bleeding, and abdominal pain (Shikhare and Kugathasan, 2010). The prevalence of IBD among children and adolescents in the United States was reported by Kappelman and colleagues and was based on a 2007 survey that collected data from 87 health plans in 33 states (Kappelman et al., 2007). For Crohn's disease, the rates for children ages 2 to <5 years and 5 to <10 years were 2.3 and 9.4 per 100,000, respectively. For ulcerative colitis, the corresponding rates were 5.4 and 8.5 per 100,000, respectively. A considerable increase in the prevalence of these IBDs was noted after the age of 10 years, at 45 and 22 per 100,000 for Crohn's disease and ulcerative colitis, respectively,

with a further increase to 85 and 58 per 100,000, respectively, for individuals ages 15 to 20 years. In 2010, Abramson and colleagues published the results of an 11-year study, reporting an increase in the incidence of both Crohn's disease and ulcerative colitis among pediatric patients enrolled in a community-based health care system (Abramson et al., 2010). The incidence of Crohn's disease rose from 2.2 to 4.3 per 100,000, and that of ulcerative colitis rose from 1.8 to 4.9 per 100,000.

Both pediatric-onset Crohn's disease and pediatric-onset ulcerative colitis have characteristics different from those of adult-onset disease. For Crohn's disease, disease at onset tends to be more severe in children than adults, necessitating a higher frequency of immunosuppressant use (Pigneur et al., 2010). In addition, the location of the disease at presentation differs from that for adult-onset disease for both Crohn's disease and ulcerative colitis (Sauer and Kugasthasan, 2010). However, as with adult-onset IBD, pediatric-onset IBD is associated with gastrointestinal symptoms, extraintestinal manifestations, and negative long-term health outcomes. The development of chronic conditions, such as joint and biliary duct diseases, as well as adverse effects on growth and bone health, all contribute to a decreased quality of life for pediatric patients, which can persist into adulthood (Sawczenko et al., 2006; Pfefferkorn et al., 2009; Turunen et al., 2009; Dotson et al., 2010; Pappa et al., 2011).

Given the significant impact of IBD on pediatric patients, effective treatment to control exacerbations is essential, as is minimizing the need for corticosteroids, which can further impede normal growth and development (Griffiths, 2009). Biologics have been shown to be an effective treatment for IBD in adults. A recent meta-analysis evaluating 27 double-blind trials (4,526 adult patients) on the use of biologics in the treatment of IBD found these agents to be effective in inducing and maintaining remission in luminal Crohn's disease and in inducing remission in ulcerative colitis (Ford et al., 2011).

However, of the biologics approved for the treatment of IBD in adults, only one is indicated for treatment of IBD (both Crohn's disease and ulcerative colitis) in pediatric patients: infliximab (Centocor Ortho Biotech, Inc., 2011). Data for the indication for Crohn's disease are primarily from the REACH trial, an open-label study enrolling 112 pediatric patients with moderate to severe, active Crohn's disease (Hyams et al., 2007; Centocor Ortho Biotech, Inc., 2011). Outcomes with long-term use of infliximab were also reported by the Pediatric Inflammatory Bowel Disease Collaborative Research Group (Hyams et al., 2009). Sustained clinical response and remission rates ranged from 64 to 83 percent and from 26 to 44 percent, respectively, during each year of follow-up. For ulcerative colitis, labeling for infliximab indicates that the efficacy of the biologic for pediatric patients is based on the results of adult clinical trials, with safety and pharmacokinetic data obtained from a study enrolling 60 pediatric patients (Centocor Ortho Biotech, Inc., 2011).

In addition to disease remission, use of infliximab was associated with improvement in markers of bone turnover, on the basis of results from an open-label extension of the REACH trial (Thayu et al., 2008). Walters and colleagues reported infliximab to increase height velocity and stature in a small group of children treated for refractory Crohn's disease (Walters et al., 2007).

The other biologic that has been evaluated in children is adalimumab, although data are limited. A retrospective review (the RESEAT trial) of data from the Pediatric

Inflammatory Bowel Disease Collaborative Research Group included 115 patients who were given at least one dose of adalimumab (Rosh et al., 2009). Clinical response rates with adalimumab at 3, 6, and 12 months were 65, 71, and 70 percent, respectively. Remission rates for the same time points ranged from 32 to 49 percent. Similar findings were reported for a small prospective study enrolling 23 patients, 14 of whom had previously been treated with infliximab (Viola et al., 2009). The 12-, 24-, and 48-week remission rates were 30.5, 50, and 65 percent, respectively. Corresponding response rates were 79, 86, and 91 percent.

Although data on the use of infliximab and, to a limited extent, adalimumab in pediatric patients are available, the role of biologics in the treatment of IBD in children remains unclear. Several advantages of biologics (primarily infliximab) have been observed, including a corticosteroid-sparing effect and improvement in growth. However, the long-term effects of these agents remain unknown, and prospective studies have been called for to evaluate the infection- and malignancy-related risks of these agents in children when given for prolonged periods of time (Rosh, 2009).

Recent guidelines on the treatment of pediatric IBD are available from the IBD Working Group of the British Society of Paediatric Gastroenterology, Hepatology, and Nutrition. These guidelines follow the typical step-up approach to therapy, placing infliximab as third-line therapy (the same level as surgery) for Crohn's disease, following failure of other agents such as corticosteroids and immunosuppressants (Sandhu et al., 2010). This approach, however, has been questioned. A top-down therapy with biologics early in the course of the disease has been suggested to reduce corticosteroid use, promote mucosal healing, avoid delays in growth, and improve quality of life in children (Cucchiara and Morelty-Fletchter, 2007; de Zoeten and Mamula, 2008).

The possible use of combination therapy with a biologic and immunosuppressants (e.g., azathioprine or 6-mercaptopurine) has also been considered. In addition to improved efficacy, concomitant use of immunosuppressants might decrease the immunogenicity of biologics (Rosh, 2009). However, adverse outcomes, including fatal hepatosplenic T-cell lymphoma, have been reported with the combination of a biologic and an immunosuppressant in young patients with IBD, making assessment of the risks and benefits of combination treatment critical (Mackey et al., 2009).

All of these concerns on the use of biologics in pediatric-onset IBD can be addressed only with well-designed clinical trials with proper attention to dose finding and understanding of the issues of extrapolation of efficacy in adults to that in children.

Oncology: Childhood Cancers

Cancer is the leading medical cause of death among children and adolescents, with a reported mortality rate of 2.3 per 100,000 (Jemal et al., 2010). Leukemias account for approximately 30 percent of newly diagnosed childhood cancers, followed by brain/central nervous system (CNS) cancers at 21 percent. The survival rate for childhood cancers has increased over the past 25 years, from 58 percent in 1975 to 81 percent in 2005. However, despite this increase in survival, research on therapy specific to pediatrics is limited. Since children and adolescents account for only a small percentage (~1 percent) of all cancer diagnoses each year, most cancer research (including research

on biologics) focuses on treatment of cancers commonly found in adults, such as breast, lung, colon, and prostate cancers (Jemal et al., 2010; Morgan, 2011).

Data from clinical trials in oncology usually cannot be extrapolated to the pediatric population because both the types and underlying biology of childhood cancers differ from those that occur in adults. The cytotoxic effects of conventional cancer therapies (e.g., alkylating agents, anthracyclines, and radiation) may have a greater impact on pediatric patients than adults and may manifest as chronic conditions (also referred to as "late effects") in adulthood (Oeffinger et al., 2006). Oeffinger and colleagues conducted a retrospective study using a cohort of 10,397 adult childhood cancer survivors and 3,034 siblings without a history of cancer to determine the incidence and severity of chronic health conditions in these groups. Among adults who had survived a childhood cancer, 62 percent had at least one chronic health condition, whereas only 36 percent of siblings did. The chronic health condition was severe, life-threatening, or disabling in 27 percent of survivors, with a relative risk of 8.2 when the incidence was compared with that in the siblings. These conditions included major joint replacement, heart failure, second malignancy, cognitive dysfunction, coronary artery disease, renal failure or need for dialysis, noncorrectable hearing or vision impairments, and ovarian failure.

Biologics are among the most advanced treatments for cancers; however, the available biologics approved for use in cancer are primarily indicated for adult solid tumor cancers rather than the malignancies most common in pediatric patients (Wickersham, 2011). Although some of these agents may be used in clinical practice, data from controlled trials on use of these agents in pediatrics are limited; some biologics have been evaluated in small, usually Phase I or II studies.

Meinhardt and colleagues evaluated the efficacy of rituximab in addition to standard chemotherapy in the treatment of new-onset mature B-cell non-Hodgkin's lymphoma or Burkitt leukemia in children and adolescents (Meinhardt et al., 2010). The primary outcome of the study was the response rate, with tolerability being a secondary outcome. A response (complete or partial) was seen in 41.4 percent of these patients. The frequent toxicities attributed to rituximab included rigors/chills, fatigue, hypotension, hematologic toxicities, infection, and nausea and vomiting. In addition, seven patients experienced an allergic reaction considered probably related to rituximab. The Children's Oncology Group also evaluated rituximab in the pediatric population for treatment of recurrent or refractory B-cell non-Hodgkin's lymphoma and mature B-cell acute lymphoblastic leukemia (Griffin et al., 2009). Sixty percent of patients had a response (complete or partial), a rate higher than the historical rate (51 percent) for usual chemotherapy without rituximab. Follow-up data reported that five patients were alive at 14 to 30 months following stem cell transplant, and four of these five patients were free of disease.

Bevacizumab has been studied in two trials for treatment of refractory solid tumors, including recurrent malignant gliomas (Glade-Bender et al., 2008; Gururangan et al., 2010). A Phase I trial enrolled 21 patients (median age, 13 years) with refractory solid tumors (excluding lymphomas or brain tumors) to evaluate the pharmacokinetics and safety of the agent (Glade-Bender et al., 2008). Although none of the treated patients experienced a response (either complete or partial), dose-limiting toxicities were not seen in any patients and treatment was generally well tolerated at doses of up to 15 mg/kg

every 2 weeks. In the second trial, bevacizumab was ineffective for the treatment of recurrent malignant or diffuse brain stem gliomas (Gururangan et al., 2010).

Finally, Trippett and colleagues conducted a Phase I trial of cetuximab in children with refractory solid tumors, including CNS tumors (Trippett et al., 2009). Diarrhea and neutropenia were dose-limiting toxicities, and both were considered to be a result of the irinotecan used concomitantly. The maximum tolerated dose of cetuximab was found to be 250 mg/m^2. Although not an objective of the study, an overall clinical benefit rate of 46.2 percent was seen among 26 patients with primary CNS tumors. The rate of anticetuximab antibody formation was also reported by the authors and was 4 percent, similar to findings for adults.

Targeted therapies with biologics have the potential to improve the prognosis of childhood cancers with historically poor outcomes (Bernstein, 2011). However, there are many unknowns regarding the use of biologics in childhood cancers. As noted above, cancers in children differ from those in adults, and these differences can alter the effects of biologics, in terms of both efficacy and adverse events. Additionally, exposure to conventional chemotherapy has long-term effects in adult survivors of childhood cancer. An important question for long-term investigation is whether exposure to biologics during childhood predisposes pediatric patients to adult-onset chronic conditions or to other cancers to a similar degree. In addition, the impact of biologics on the growth and development of children is unknown.

Endocrinology: Diabetes

Both type 1 and type 2 diabetes can have a significant impact on quality of life in children (American Diabetes Association, 2011). Although the incidence of type 2 diabetes in children is increasing, in part because of the rise in the incidence of obesity among children, the onset is more common in adulthood. In contrast, the onset of type 1 diabetes is frequently seen during childhood. One epidemiologic study reported that approximately 26 percent of cases of type 1 diabetes presented in children less than 4 years of age and 37 percent presented at 5 to 14 years of age (Harjutsalo et al., 2008). However, the frequency of diabetic ketoacidosis at onset of the disease is higher in younger children (40 to 50 percent for ages 0 to 4 years) than in older adolescents (12 to 15 percent for ages 15 to 21 years) (Daneman, 2006). Type 1 diabetes accounts for only 5 to 10 percent of all cases of diabetes; but its early onset, faster and more intense destruction of pancreatic β cells (compared with type 2 diabetes), and association with short- and long-term complications make it a serious, chronic disorder of importance among children.

Type 1 diabetes results from destruction of pancreatic β cells resulting from a cell-mediated autoimmune reaction (Daneman, 2006). This then causes a progressive loss of insulin production; patients eventually have an absolute insulin deficiency, requiring exogenous insulin to maintain glucose hemostasis. Although insulin is an effective treatment and the new analog insulins allow greater physiologic control of glucose, complications from treatment can still frequently occur. In the short term, hypoglycemia is likely the most important complication of type 1 diabetes, which can be life-threatening and can interfere with effective glucose control. Side effects of insulin in both adults and

children can include hypersensitivity reactions, lipohypertrophy or -atrophy, and pain at the injection site (Bangstad et al., 2007). Long-term diabetes is associated with micro- and macrovascular complications, including nephropathy, retinopathy, and cardiovascular disease (Daneman, 2006). Some of these complications, such as retinopathy, may be seen early in the course of the disease (Maguire et al., 2005).

Given the role of the immune system in the development of type 1 diabetes, studies have looked at the effects of monoclonal antibodies—primarily CD3-specific antibodies—on the preservation of β-cell function (Kaufman and Herold, 2009). Otelixizumab, an investigational CD3 surface antigen antibody, was evaluated for its effects on new-onset type 1 diabetes (Keymeulen et al., 2005). The CD3 surface antigen was targeted because of the T-cell-mediated autoimmune mechanism of type 1 diabetes. Residual β-cell function (as measured by C-peptide release) was maintained among patients given otelixizumab and returned to baseline at 18 months after treatment. Patients given placebo had reductions in β-cell function of just over 30 percent during the same time period. In addition, treatment with the monoclonal antibody had a greater effect in patients with higher residual β-cell function at baseline (≥50th percentile). Adverse effects of treatment were transient but significant, with nearly all treated patients experiencing fever, headache, gastrointestinal events, arthralgia, myalgia, rash, and an acute mononucleosis-like syndrome.

A second investigational anti-CD3 monoclonal antibody, teplizumab, was evaluated in 24 patients with a diagnosis of type 1 diabetes of 6 weeks or less (Herold et al., 2002). Teplizumab or placebo was given as a 14-day course of treatment, and patients were assessed after 1 year. The monoclonal antibody significantly attenuated the decline in C-peptide response compared with placebo. A decline in both glycosylated hemoglobin (A1C) levels and insulin dose were also seen with teplizumab. Similar results were reported in a 2-year follow-up; the effects of teplizumab were maintained (Herold et al., 2005).

A second trial of teplizumab was initiated with patients with recent-onset type 1 diabetes (Herold et al., 2009). This study, however, was stopped after enrollment of 10 patients (6 given teplizumab) due to a substantially higher rate of adverse events than previously seen, despite use of the same dosage regimen (Herold et al., 2002, 2005). It was later determined that a change in the manufacturing of teplizumab—use of a stoppered vial instead of a glass ampoule—resulted in a 40 percent increase in the dose of teplizumab over previous trials and a subsequent increase in adverse events (Herold et al., 2009). During preparation for administration, the contents of the glass ampoule were filtered, whereas a filter was not used when the agent was packaged in a stoppered vial. An extended follow-up of patients given teplizumab was conducted. At 60 months, the mean loss of baseline function (based on C-peptide response) was 63.8 percent, indicating that the monoclonal antibody had a prolonged effect.

A more recent, larger study of teplizumab enrolled 516 patients (ages 8 to 35 years) with type 1 diabetes within 12 weeks from diagnosis (Sherry et al., 2011). Results of the trial did not show an effect on β-cell preservation at 1 year. However, an exploratory analysis on the effect of teplizumab in the children suggested a better C-peptide response, findings that need to be confirmed.

In addition to CD3-specific antibodies, rituximab, an anti-CD20 monoclonal antibody, has been evaluated for preservation of β-cell function (Pescovitz et al., 2009).

At 1 year after treatment, a significantly lesser decline in the level of C peptide (as a marker of β-cell function) from baseline was seen with rituximab than placebo, and the decline was accompanied by reductions in both A1C and total insulin use. Adverse events occurred significantly more often with the use of rituximab than placebo, including fever, rash, hypotension, nausea, fever, and tachycardia.

Overall, immunotherapy seems to be a promising area for research. As a life-long disease, the safety of biologics in the treatment of type 1 diabetes in children is of utmost importance. On the basis of the available data, treatment must be initiated shortly after diagnosis (before extensive loss of β-cell function) to preserve endogenous insulin production. However, the effects of biologics on growth and development of young children are largely unknown. Additionally, since a single course of therapy with a biologic may have a prolonged effect on β-cell preservation, the optimal frequency of treatment needs to be established. Finally, another critical question for evaluation is whether the risks associated with biologics outweigh the benefits of delaying or minimizing the long-term complications of type 1 diabetes.

CONCLUSION

For many disease states, biologics represent the most advanced therapeutic approach. The use of biologics for chronic conditions such as rheumatoid arthritis, psoriasis, and IBD has been established in adults. These agents have improved the quality of life of adult patients with these and similar immune-mediated diseases and induce a remission of symptoms for some diseases. However, the role of biologics (excluding plasma-derived or recombinant factor proteins) in many pediatric disease states is less clear. Most data on biologics appear to be for JIA, with some biologics approved for children as young as 2 years of age. IBD, atopic dermatitis, psoriasis, childhood cancers, and type 1 diabetes—the conditions discussed in this paper—all have a significant impact on the quality of life of children, which in many cases extends to adulthood. Taking prevalence, burden of disease, and life expectancy as well as a lack of pediatric studies into account, the two areas in which research in biologics may be the most needed are childhood cancers and type 1 diabetes.

For childhood cancers, use of many therapies is extrapolated from data for adults because of the limited availability of data for the pediatric population. Although childhood cancers represent only about 1 percent of all cancers, they are the leading medical cause of death among children, making improvements to the survival of these patients a priority. Additionally, the cure of a childhood cancer prolongs life not by 10 or 20 years, as in adults, but potentially by 60 or 70 years, balancing any higher therapeutic costs with a substantial gain in life-years.

Also important is type 1 diabetes. Although type 1 diabetes accounts for only 5 to 10 percent of cases of diabetes, nearly half of these cases are diagnosed in childhood. The only effective therapy is insulin, and despite appropriate treatment, type 1 diabetes is associated with significant morbidity and mortality from micro- and macrovascular complications. Preliminary data suggest that early intervention with biologics has the potential to preserve β-cell function and endogenous insulin secretion (Herold et al., 2005; Keymeulen et al., 2005; Kaufman et al., 2009; Pescovitz et al., 2009). This could

potentially prevent or limit the long-term complications of the disease and greatly improve the quality of life of patients with type 1 diabetes. Although biologic therapy is likely to be more costly than current insulin therapies, the cost of biologic therapy in childhood may be offset by the benefits of decreased morbidity in adulthood.

A major concern about which little is known is the effect, if any, that biologics can have on childhood development and growth or if negative effects of treatment may be seen in adulthood. As noted above, some established treatments used with children may potentially increase the risk of subsequent malignancies. In addition to well-designed clinical trials, establishment and continued use of registry data are important for investigation of the long-term effects of biologics.

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D
Biologics Studied and Not Studied in Children*

To identify biologics that have been studied, were being studied, or were planned for study in children, the Institute of Medicine committee examined several sources of information about biologics that were approved by the Food and Drug Administration (FDA) after January 1, 1997, and that are still marketed in the United States.[1] FDA supplied the list of biologics for products now regulated by the Center for Drug Evaluation and Research (CDER). For the biologics that are regulated by the Center for Biologics Evaluation and Research (CBER), the committee relied on a website listing biologics for which some supporting documentation was available.

As explained in Chapter 8, the committee excluded preventive vaccines and nontherapeutic biologics such as assays and reagents (e.g., products used for blood testing or blood grouping). It also excluded products that were approved before 1997, were approved under new drug applications, were not approved for marketing in the United States, had been withdrawn from the market, or were not new products. The final list included 97 biologics. Of these, 58 were regulated by CDER and 39 were regulated by CBER. This appendix reports information from the labeling of these products and from a government registry of clinical trials.

Although the committee excluded vaccines for its more extensive analysis, it conducted a less intensive review of information on pediatric studies and labeling for vaccines. It identified vaccines with supporting information that CBER has posted at http://www.fda.gov/BiologicsBloodVaccines/ucm133705.htm. The vaccines listed include some that were approved before 1997, although the committee sometimes found it difficult to identify original approval dates.

A number of vaccines (e.g., vaccines for rotavirus and combination vaccines for diphtheria, tetanus, and pertussis) are labeled for pediatric use only. Of the 55 vaccines listed by CBER, three products (5 percent) were not labeled for pediatric use, had waivers of pediatric study requirements, and did not have pediatric studies registered at ClinicalTrials.gov.

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[1] The original approval dates for biologics are not always easily determined. It is possible that one or more of the products listed had an original approval date prior to 1997.

- An adenovirus type 4 and type 7 vaccine (no brand name) was developed under contract with the U.S. Department of Defense and approved by FDA in 2011 for use with military personnel ages 17 to 50 years; an earlier product had been used by the military beginning in the 1980s and ending after the sole manufacturer stopped manufacturing the product (Schrager, 2011). FDA waived the pediatric study requirement because studies were impossible or impractical (Malarkey and Baylor, 2011).[2]
- An anthrax vaccine (no brand name) was approved in 2002 for use by individuals ages 18 to 65 years who are at high risk of exposure to the disease. In a 2008 approval for a new dosing interval and route of administration, FDA waived the pediatric study requirement on the grounds that studies were impossible or impracticable because the pediatric population is not at high risk of exposure (Sun, 2008).
- A herpes zoster (shingles) vaccine (Zostamax) was approved by FDA in 2006 for use by individuals 60 years of age or older. FDA waived the requirement for pediatric studies because the product did not offer a meaningful therapeutic benefit over existing products and was unlikely to be used by a substantial number of children (Baylor, 2006).

In addition, FDA waived pediatric studies (without explanation) in approving a vaccine (Twinrix) for prevention of hepatitis A and B (Richman, 2007). For this product, however, ClinicalTrials.gov lists pediatric studies (see, e.g., ClinicalTrials.gov identifier: NCT00107042). For an interdermal formulation of an influenza vaccine (Fluzone), FDA waived pediatric studies because the product did not offer a meaningful therapeutic benefit over existing products and was unlikely to be used by a substantial number of children (Sun, 2011). ClinicalTrials.gov also lists pediatric studies of this product (see, e.g., ClinicalTrials.gov identifier: NCT00391391).

For the biologics including in the committee's more extensive investigation, the committee consulted the current product labeling for references to pediatric studies; approval letters, if available for references to required pediatric studies; FDA's tracking database for postmarket study requirements and commitments; and ClinicalTrials.gov. ClinicalTrials.gov is a registry of publicly and privately supported clinical trials that is administered by the National Institutes of Health.

Table D-1, which groups CDER- and CBER-regulated products together, summarizes pediatric information found in the manufacturer's current product labeling. This information includes any pediatric use(s) for which the product is labeled; descriptions in the labeling of pediatric studies of the product (including studies that did not demonstrate efficacy); and, for any products without such labeling information, any warnings against pediatric use based on FDA or other analyses of adverse event reports or similar data. Information relevant to use of a product by pediatric populations may be located in several sections of the structured label (e.g., in sections on dosage, clinical pharmacology, and adverse reactions as well as in the highlights section that now appears at the start of prescription labeling). This can complicate efforts to find and summarize this information. Most of the review of labeling occurred in July and August, 2011.

Table D-2 summarizes information about pediatric studies registered at the ClinicalTrials.gov database. It first presents the information for CDER-regulated products and then presents the information for CBER-regulated products. For this table, products

[2] References cited in this appendix are included in the report's reference list.

in certain classes (e.g., intravenous immune globulins) that are often treated as interchangeable for certain uses were grouped together because database entries often did not identify studied products by brand name. Trials for which the lower age range was 16 years are not included. The database was checked from July to December, 2011.

The brief summaries in the trials database were sometimes incorrect in indicating that a trial included children, particularly when the more detailed trial descriptions did not include an overview description of the age range but did make clear in the inclusion or exclusion criteria that only adults were eligible. Summaries could also be misleading about the condition to be studied, for example, by specifying transplantation rather than transplantation-related complications or disorders. A study categorized in the database as a Phase IV study, particularly one requested under the Best Pharmaceuticals for Children Actor or required under the Pediatric Research Equity Act, might also fit the definition of a Phase I, II, or III study.

TABLE D-1 Labeling Information on Pediatric Uses, Studies, and Certain Safety Warnings for Still-Marketed Biologics Approved After January 1, 1997 (products are listed alphabetically for CDER- and CBER-regulated products combined)

Generic Name (Trade Name) (BLA Number) Original Approval Date	Approved Indication(s)	Highlights of Pediatric Information in Labeling
1. Abatacept (Orencia) (125118) 12/23/2005	• Adult rheumatoid arthritis • Juvenile idiopathic arthritis (JIA)	*Labeled pediatric use(s)* • ≥6 yr with moderately to severely active polyarticular JIA; may be used as monotherapy or concomitantly with methotrexate • Not established in patients <6 yr • Not established for diseases other than JIA *Study information* • Safety and efficacy were assessed in patients 6 to 17 yr (*n* = 190). • Findings showed that the risk of disease flare in patients on Orencia was <1/3 the risk for flare in patients withdrawing from Orencia. • Infections were the most frequent adverse events.
2. Abobotulinumtoxin A (Dysport) (125274) 04/29/2009	• Cervical dystonia • Temporary improvement in glabellar lines	Not established in pediatric patients with cervical dystonia Not recommended for patients <18 yr for glabellar lines

Generic Name (Trade Name) (BLA Number) Original Approval Date	Approved Indication(s)	Highlights of Pediatric Information in Labeling
3. Adalimumab (Humira) (125057) 12/31/2002	• Rheumatoid arthritis • Juvenile idiopathic arthritis (JIA) • Psoriatic arthritis • Ankylosing spondylitis • Crohn's disease • Plaque psoriasis	*Labeled pediatric use(s)* • Patients 4 to 17 yr for JIA • Unestablished for children weighing <15 kg • Unestablished for disease states other than JIA *Study information* • Safety and efficacy were assessed in patients 4 to 17 yr (n = 171). • Findings showed fewer patients in the adalimumab group than in placebo group experienced disease flare, regardless of methotrexate use. • Malignancies have been reported in children and adolescent patients receiving treatment with tumor necrosis factor blockers, of which adalimumab is a member. • Injection site reactions and infections are common adverse events.
4. Agalsidase beta (Fabrazyme) (103979) 04/24/2003	Fabry disease	*Labeled pediatric use(s)* • Patients 8 to 16 yr with Fabry disease • Not established for use in children <8 yr *Study information* • Safety, pharmacokinetics, and pharmacodynamics were assessed in patients 8 to 16 yr (n = 16). • Ten of 12 patients taking agalsidase beta had a reduction in globotriaosylceramide to normal levels. • No new safety concerns were identified in pediatric patients. • Infusion reactions were the most common adverse event.
5. Albumin (human) (Albumin) (125154) (10/17/2006)	• Hypovolemia • Hypoalbuminemia • Prevention of central volume depletion after paracentesis	*Labeled pediatric use(s)* • Albumin should be administered to pediatric patients only if necessary. *Study information* • Data on use of 5% albumin in children and premature babies are limited.
6. Alefacept (Amevive) (125036) 1/30/2003	Chronic plaque psoriasis in adult patients	Safety and efficacy of Amevive in pediatric patients have not been studied.
7. Alemtuzumab (Campath) (103948) 05/07/2001	B-cell chronic lymphocytic leukemia	Safety and effectiveness in pediatric patients have not been established.
8. Alglucosidase alfa (Lumizyme) (125291) 05/24/2010	Late-onset Pompe disease (α-glucosidase deficiency)	*Labeled pediatric use(s)* • Patients >8 yr with late-onset Pompe disease *Study information* • Safety and efficacy in pediatric patients have not been evaluated in clinical trials.

Generic Name (Trade Name) (BLA Number) Original Approval Date	Approved Indication(s)	Highlights of Pediatric Information in Labeling
9. Alglucosidase alfa (Myozyme) (125141) 04/28/2006	Pompe disease (α-glucosidase deficiency)	*Labeled pediatric use(s)* • Infantile-onset Pompe disease (improvement in ventilator-free survival) *Study information* • Efficacy was assessed in patients ≤7 mo with infantile-onset Pompe disease (*n* = 18). • A greater survival without invasive ventilator support was seen in patients receiving alglucosidase alfa vs. historical control. • Efficacy was assessed in patients 3 mo to 3.5 yr (*n* = 21). • No effect of alglucosidase alfa compared with control could be determined. • Most common adverse reactions were infusion related. • Anaphylactic reactions, cardiorespiratory failure, and cardiac arrest have also occurred.
10. Alpha1-proteinase inhibitor (human) (Aralast NP) (125039) 05/04/2007	Congenital deficiency of α_1-proteinase inhibitor with clinically evident emphysema	Safety and effectiveness in pediatric patients have not been established.
11. Alpha1-proteinase inhibitor (human) (Glassia) (125325) 07/01/2010	Emphysema due to congenital deficiency of α_1-proteinase inhibitor	Safety and effectiveness in pediatric patients have not been established.
12. Alpha1-proteinase inhibitor (human) (Zemaira) (125078) (07/08/2003)	Congenital deficiency of α_1-proteinase inhibitor with clinically evident emphysema	Safety and effectiveness in pediatric patients have not been established.
13. Anakinra (Kineret) (103950) 11/14/2001	Rheumatoid arthritis in adults	Not recommended because prefilled syringes do not allow accurate dosing below 100 mg and efficacy could not be demonstrated in study because of low enrollment *Study information* • Efficacy was assessed in patients 2 to 17 yr (*n* = 86) with juvenile rheumatoid arthritis. • Efficacy was not demonstrated. An adverse event profile similar to that seen in adult patients with rheumatoid arthritis was observed.
14. Antihemophilic factor (recombinant) (ReFacto) (103779) 03/06/2000	• Control and prevention of hemorrhagic episodes and for surgical prophylaxis in patients with hemophilia A • Short-term prophylaxis of spontaneous bleeding episodes in patients with hemophilia A	*Labeled pediatric use(s)* • Appropriate for use in children of all ages with hemophilia A, including newborns. *Study information* • Safety and efficacy studies have been performed with previously untreated neonates, infants, and children <1 to 52 mo (*n* = 101). • Studies were also performed with previously treated children and adolescents 5 to 18 yr (*n* = 31).

Generic Name (Trade Name) (BLA Number) Original Approval Date	Approved Indication(s)	Highlights of Pediatric Information in Labeling
15. Antihemophilic factor (recombinant), plasma/albumin free (Xyntha) (125264) 02/21/2008	• Control and prevention of bleeding episodes in patients with hemophilia A • Surgical prophylaxis in patients with hemophilia A	*Labeled pediatric use(s)* • Bleeding episodes in hemophilia A • Surgical prophylaxis in hemophilia A • Description of indicated uses does not mention pediatric population explicitly. *Study information* • Pharmacokinetics were studied in previously treated patients 12 to 16 yr (n = 7). • Pharmacokinetic parameters were similar to those observed in adults.
16. Antihemophilic factor (recombinant), plasma/albumin-free method (Advate) (125063) 07/25/2003	• Control and prevention of bleeding episodes in adults and children with hemophilia A • Perioperative management in adults and children with hemophilia A	*Labeled pediatric use(s)* • Control and prevention of bleeding episodes in adults and children with hemophilia A • Perioperative management in adults and children with hemophilia A *Study information* • Pharmacokinetic studies were performed in patients 1 mo to <16 yr (n = 51). • In comparison with adults, children had higher Factor VIII clearance values and thus lower half-lives and recovery of Factor VIII. • Larger or more frequent doses should be considered in a pediatric patient population
17. Antithrombin (recombinant) (ATryn) (125284) 02/06/2009	• Prevention of perioperative and peripartum thromboembolic events in hereditary antithrombin-deficient patients • Not indicated for treatment of thromboembolic events in hereditary antithrombin-deficient patients	Safety and effectiveness in pediatric patients have not been established.
18. Anti-thymocyte globulin (rabbit) (Thymoglobulin) (103869) 12/30/1998	Acute rejection in renal transplant patients	Safety and effectiveness in pediatric patients have not been established in controlled trials. *Study information* • Dose, efficacy, and adverse event profile are thought to be similar to those in adults, based on limited European studies and U.S. compassionate use.
19. Autologous cultured chondrocytes (Carticel) (103661) 08/22/1997	Repair of symptomatic cartilage defects of the femoral condyle	Safety and effectiveness in pediatric patients have not been established.

Generic Name (Trade Name) (BLA Number) Original Approval Date	Approved Indication(s)	Highlights of Pediatric Information in Labeling
20. Basiliximab (Simulect) (103764) 05/12/1998	Prophylaxis of acute organ rejection in patients receiving renal transplantation	Safety and effectiveness in pediatric patients have not been established. *Study information* • Safety and pharmacokinetics were assessed in patients 12 to 16 yr (*n* = 41) • The adverse event profile was consistent with general clinical experience in pediatric renal transplantation population and with the profile in controlled adult renal transplantation studies
21. Becaplermin (Regranex) (103691) 12/16/1997	Lower-extremity diabetic neuropathic ulcers	Safety and effectiveness in pediatric patients below 16 yr have not been established.
22. Bevacizumab (Avastin) (125085) 02/26/2004	• Metastatic colorectal cancer • Nonsquamous non-small-cell lung cancer • Metastatic breast cancer • Glioblastoma • Metastatic renal cell carcinoma	Safety, effectiveness, and pharmacokinetic profile in pediatric patients have not been established.
23. Botulism immune globulin intravenous (human) (BabyBIG) (125034) 10/23/2003	Treatment of infant botulism by toxin types A or B in patients <1 yr	*Labeled pediatric use(s)* • Treatment of infant botulism by toxin type A or B in patients <1 yr • BabyBIG has not been tested in other populations. *Study information* • Efficacy and safety were assessed in an infant population (*n* = 129). • BabyBIG was shown to significantly reduce hospital and intensive care unit stays, mechanical ventilation, and tube feeding. • The only noted adverse event was a mild rash on the face or trunk.
24. C1 esterase inhibitor (Cinryze) (125267) 10/10/2008	Routine prophylaxis against angioedema attacks in adolescent and adult patients with hereditary angioedema (HAE)	*Labeled pediatric use(s)* • Prophylaxis of attacks of HAE in adolescent and adult patients • Safety and effectiveness in neonates, infants, or children have not been established. *Study information* • Three adolescent patients were included in a routine prophylaxis trial that found Cinryze to be effective in reducing days of swelling and mean severity and duration of attacks.
25. C1 esterase inhibitor (human) (Berinert) (125287) 10/09/2009	Treatment of acute abdominal or facial attacks of hereditary angioedema (HAE) in adult and adolescent patients	*Labeled pediatric use(s)* • Treatment of attacks of HAE in patients >12 yr • Safety and efficacy in patients 0 to 12 yr have not been established. *Study information* • Pharmacokinetics, safety, and efficacy were established in patients 3 to 12 yr (*n* = 5) and 13 to 16 yr (*n* = 8).

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26. Canakinumab (Ilaris) (125319) 06/17/2009	Cryopyrin-associated periodic syndromes (CAPS) in adults and children ≥4 yr: • Familial cold autoinflammatory syndrome • Muckle-Wells syndrome	*Labeled pediatric use(s)* • CAPS in patients ≥4 yr • Safety and effectiveness of Ilaris in patients under 4 yr have not been established. *Study information* • Safety and efficacy were assessed in the CAPS trial in patients 4 to 17 yr (*n* = 23). • The majority of patients achieved improvement in clinical symptoms and objective markers of inflammation. • Overall safety and efficacy of canakinumab in pediatric patients were comparable to those in adults.
27. Certolizumab pegol (Cimzia) (125160) 04/22/2008	• Crohn's disease • Rheumatoid arthritis	Safety and effectiveness in pediatric patients have not been established. *Boxed warning* • Lymphoma and other malignancies, some fatal, have been reported in children and adolescent patients treated with tumor necrosis factor blockers, of which certolizumab is a member. Certolizumab is not indicated for use in pediatric patients.
28. Cetuximab (Erbitux) (125084) 02/12/2004	• Squamous cell carcinoma of the head and neck • Metastatic colorectal cancer	Safety and effectiveness in pediatric patients have not been established. *Study information* • Pharmacokinetics were assessed in patients 1 to 12 yr (*n* = 27) and 13 to 18 yr (*n* = 19). • Pharmacokinetic profiles were similar between the age groups. • No new safety signals were identified in pediatric patients.
29. Coagulation Factor VIIa (recombinant) (NovoSeven) (103665) 03/25/1999	• Treatment of bleeding episodes in patients with hemophilia A or B and in acquired hemophilia • Prevention of bleeding in surgical interventions or invasive procedures in patients with hemophilia • Treatment of bleeding episodes in patients with congenital Factor VII deficiency • Prevention of bleeding in surgical interventions or invasive procedures in patients with Factor VII deficiency	*Labeled pediatric use(s)* • The safety and effectiveness of NovoSeven was not determined to be different in various age groups, from infants to adolescents (0 to 16 years of age). *Study information* • Clinical trials enrolling pediatric patients were conducted, with dosing determined according to body weight and not according to age.

Generic Name (Trade Name) (BLA Number) Original Approval Date	Approved Indication(s)	Highlights of Pediatric Information in Labeling
30. Coagulation Factor IX (recombinant) (Benefix) (103677) 02/01/1997	• Control and prevention of bleeding episodes in adult and pediatric patients with hemophilia • Perioperative management in adult and pediatric patients with hemophilia	*Labeled pediatric use(s)* • Control and prevention of bleeding episodes in pediatric patients with hemophilia • Perioperative management in pediatric patients with hemophilia *Study information* • Pharmacokinetics, safety, and efficacy have been assessed in pediatric patients. • A lower recovery is generally observed for patients <15 yr; a dose adjustment may be needed.
31. Collagenase *Clostridium histolyticum* (Xiaflex) (125338) 02/02/2010	Adult patients with Dupuytren's contracture	Safety and effectiveness in pediatric patients have not been established.
32. Crotalidae polyvalent immune Fab (ovine) (CroFab) (103788) 10/02/2000	Management of patients with North American crotalid (venomous snakes) envenomation	*Labeled pediatric use(s)* • Specific studies with pediatric patients have not been conducted. The absolute venom dose following snakebite is expected to be the same in children and adults; therefore, no dosage adjustment for age should be made. *Study information* • Two clinical trials using CroFab have been conducted. They were prospectively defined, open-label, multicenter trials conducted with otherwise healthy patients 11 yr or older who had suffered from minimal or moderate North American crotalid envenomation that showed evidence of progression.
33. Daclizumab (Zenapax) (103749) 12/10/1997	Prophylaxis of acute organ rejection in patients receiving renal transplants	*Labeled pediatric use(s)* • Prophylaxis of acute organ rejection in patients 11 mo to 17 yr receiving renal transplants *Study information* • Pharmacokinetics, efficacy, immunogenicity, and safety were assessed in patients 11 mo to 17 yr (n = 60). • Patient and graft survival at 1 yr posttransplant were 100% and 96.7%, respectively. • Incidence of antidaclizumab antibodies (34%) was higher than incidence previously observed in adult patients. • Safety profile in pediatric population was comparable to that in adult patients, with some exceptions.

Generic Name (Trade Name) (BLA Number) Original Approval Date	Approved Indication(s)	Highlights of Pediatric Information in Labeling
34. Darbepoetin alfa (Aranesp) (103951) 09/17/2001	Treatment of anemia due to chronic kidney disease (CKD) or myelosuppressive chemotherapy	*Labeled pediatric use(s)* • Treatment of anemia due to CKD in patients >1 yr and currently being treated with epoeitin alfa • Safety and efficacy have not been assessed in initial treatment of anemic pediatric patients with CKD. • Safety and efficacy in pediatric cancer patients have not been established. *Study information* • Pharmacokinetics were assessed in patients 3 to 16 yr (*n* = 12). • Pharmacokinetic parameters were similar to those obtained in adult patients. • Safety and the ability of darbepoetin to maintain hemoglobin concentrations in patients who had been receiving other recombinant erythropoietins were assessed in patients 1 to 17 yr (*n* = 123). • Efficacy and safety in the pediatric population were similar to those in the adult population.
35. Denileukin diftitox (Ontak) (103767) 02/05/1999	Cutaneous T-cell lymphoma	Safety and efficacy in pediatric patients have not been established.
36. Denosumab (Prolia/Xgeva) (125320) 06/01/2010	Xgeva: prevention of skeleton-related events in patients with bone metastases from solid tumors Prolia: treatment of postmenopausal women with osteoporosis	Safety and effectiveness of denosumab in pediatric patients have not been established. Its use is not recommended in pediatric patients, as it may impair bone growth and may inhibit eruption of dentition.
37. Digoxin immune Fab (ovine) (DigiFab) (103910) 08/31/2001	Treatment of patients with life-threatening or potentially life-threatening digoxin toxicity or overdose	A similar digoxin ovine Fab product, Digibind, has been used successfully to treat infants. As with all drugs, the use of DigiFab in infants and children should be based on careful consideration of the benefits compared with the potential risks. *Study information* • No pediatric patients were enrolled in clinical studies of DigiFab.
38. Ecallantide (Kalbitor) (125277) 11/27/2009	Acute attacks of hereditary angioedema (HAE)	Safety and effectiveness of Kalbitor in patients <16 yr have not been established. *Study information* • No studies with a pediatric population have been completed.
39. Eculizumab (Soliris) (125166) 03/16/2007	Paroxysmal nocturnal hemoglobinuria to reduce hemolysis	Safety and effectiveness in pediatric patients <18 yr have not been established.

Generic Name (Trade Name) (BLA Number) Original Approval Date	Approved Indication(s)	Highlights of Pediatric Information in Labeling
40. Etanercept (Enbrel) (103795) 11/02/1998	• Rheumatoid arthritis (RA) • Polyarticular juvenile idiopathic arthritis (JIA) in patients >2 yr • Psoriatic arthritis • Ankylosing spondylitis • Plaque psoriasis	*Labeled pediatric use(s)* • Polyarticular JIA in patients >2 yr • Not established for JIA in patients <2 yr • Safety and efficacy for plaque psoriasis in pediatric patients have not been established. *Study information* • Safety and efficacy were assessed in patients 2 to 17 yr patients with JIA (n = 69). • Significantly fewer patients who remained on etanercept than those who were on placebo experienced disease flare. *Boxed warning* • Lymphoma and other malignancies, some fatal, have been reported in children and adolescent patients treated with tumor necrosis factor blockers, including etanercept.
41. Fibrin sealant (TachoSil) (125351) (04/02/2010)	Adjunct to hemostasis for use in cardiovascular surgery	Safety and effectiveness in pediatric patients undergoing cardiovascular surgery have not been established.
42. Fibrin sealant (Tisseel) (103980) 05/01/1998	Adjunct to hemostasis in surgeries involving • Cardiopulmonary bypass • Treatment of splenic injuries	Safety and effectiveness in pediatric patients have not been established.
43. Fibrin sealant (human) (Artiss) (125266) 03/21/2008	To adhere autologous skin grafts to surgically prepared wound beds resulting from burns in adult and pediatric populations	*Labeled pediatric use(s)* • Adherence of skin grafts to burns in patients ≥1 yr *Study information* • Safety and efficacy were assessed in patients 1 to 16 yr (n = 36). • Safety and efficacy did not differ from those in an adult population.
44. Fibrin sealant (human) (Evicel) (125010) 03/21/2003	Adjunct to hemostasis for use in patients during surgery	*Labeled pediatric use(s)* • Adjunct to hemostasis for use in patients >6 mo during surgery *Study information* • No data were available for patients 0 to 6 mo. • Four pediatric patients were included in a study assessing use during retroperitoneal and intra-abdominal surgery; eight pediatric patients were included in a study assessing use during liver surgery. • On the basis of these data, use of Evicel in a pediatric population is supported.
45. Fibrinogen concentrate (human) (RiaSTAP) (125317) 01/16/2009	Treatment of acute bleeding episodes in patients with congenital fibrinogen deficiency	*Labeled pediatric use(s)* • Statement of indicated use does not explicitly refer to pediatric patients *Study information* • Studies included patients <16 yr. • Patients <16 yr had shorter half-lives and faster clearance than adults.

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46. Galsulfase (Naglazyme) (125117) 05/31/2005	Mucopolysaccharidosis VI (MPS VI; Maroteaux-Lamy syndrome)	*Labeled pediatric use(s)* • MPS VI in patients ≥5 yr • Safety and efficacy in patients <5 yr have not been established. *Study information* • Clinical studies have been performed with patients 5 to 29 yr (n = 56). • Findings showed galsulfase to be effective at improving endurance in comparison with placebo. • An open-label study was conducted with four infants. • Safety results are consistent with results for patients 5 to 29 yr.
47. Golimumab (Simponi) (125289) 04/24/2009	• Rheumatoid arthritis • Psoriatic arthritis • Ankylosing spondylitis	Safety and effectiveness of golimumab in pediatric patients <18 yr have not been established. *Boxed warning* • Lymphoma and other malignancies, some fatal, have been reported in children and adolescent patients treated with tumor necrosis factor blockers, of which golimumab is a member.
48. Hepatitis B immune globulin (human) (Nabi-HB) (103945) 10/23/2001	Treatment of • Acute exposure to blood containing hepatitis B virus (HBV) surface antigen (HBsAg) • Perinatal exposure of infants born to HBsAg-positive mothers • Sexual exposure to HBsAg-positive persons • Household exposure to persons with acute HBV infection	*Labeled pediatric use(s)* • Perinatal exposure of infants born to HBsAg-positive mothers • Infants less than 12 mo old whose mother or primary caregiver is positive for HBsAg *Study information* • Safety and efficacy in the pediatric population have not been established. However, safety and effectiveness of similar hepatitis B immune globulins have been demonstrated in infants and children.
49. Hepatitis B immune globulin intravenous (human) (HepaGam B) (125237) 04/06/2007	• Prevention of hepatitis B following liver transplantation • Postexposure prophylaxis in the following settings: acute exposure to blood containing hepatitis B virus (HBV) surface antigen (HBsAg), perinatal exposure of infants born to HBsAg-positive mothers, sexual exposure to HBsAg-positive persons, household exposure to persons with acute HBV infection	*Labeled pediatric use(s)* • Perinatal exposure of infants born to HBsAg-positive mothers • Safety and effectiveness have not been established in pediatric patients. However, for postexposure prophylaxis, the safety and effectiveness of similar hepatitis B immune globulins have been demonstrated in infants and children.

Generic Name (Trade Name) (BLA Number) Original Approval Date	Approved Indication(s)	Highlights of Pediatric Information in Labeling
50. Ibritumomab tiuxetan (Zevalin) (125019) 02/19/2002	• Low-grade B-cell non-Hodgkin's lymphoma (NHL) • Follicular NHL	Safety and effectiveness of Zevalin in pediatric patients have not been established.
51. Idursulfase (Elaprase) (125151) 07/24/2006	Hunter syndrome (Mucopolysaccharidosis II [MPS II])	*Labeled pediatric use(s)* • Hunter syndrome in patients ≥5 yr • Safety and efficacy in pediatric patients <5 yr have not been established. *Study information* • Safety and efficacy have been evaluated in patients 5 to 31 yr (*n* = 96). • Findings showed improved walking capacity in patients receiving idursulfase compared with that in patients receiving placebo. • Children, adolescents, and adults responded similarly to treatment with idursulfase. • Adverse effects include infusion-related reactions and hypoxemic episodes.
52. Immune globulin injection (human), 10%, caprylate/chromatography purified (Gamunex-C) (125046) 08/27/2003	• Primary humoral immunodeficiency (PI) • Idiopathic thrombocytopenic purpura (ITP) • Chronic inflammatory demyelinating polyneuropathy (CIDP)	*Labeled pediatric use(s)* • PI (intravenous route) in pediatric patients • ITP (intravenous route) in pediatric patients • Efficacy and safety of CIDP in pediatric patients have not been established. • Efficacy and safety by the subcutaneous route in pediatric patients have not been established. *Study information* • Intravenous Gamunex-C was evaluated for treatment of PI in pediatric patients 0 to 16 yr (*n* = 18). • Pharmacokinetics, safety, and efficacy were similar to those in an adult population. • Vomiting was more frequent in the pediatric population. • Subcutaneous Gamunex-C was evaluated in three pediatric patients with PI; this number was too small to evaluate them separately from an adult population. • Intravenous Gamunex-C was evaluated for the treatment of ITP in pediatric patients (*n* = 12). • Pharmacokinetics, safety, and efficacy were similar to those in an adult population. • Fever was more frequent in the pediatric population.
53. Immune globulin intravenous (human) (Flebogamma, 5% DIF) (125077) 12/15/2003	Treatment of primary humoral immunodeficiency disorders	Efficacy and safety in pediatric patients have not been established.

Generic Name (Trade Name) (BLA Number) Original Approval Date	Approved Indication(s)	Highlights of Pediatric Information in Labeling
54. Immune globulin intravenous (human), 5% liquid (Octagam) (125062) 05/21/2004	Treatment of primary humoral immunodeficiency	*Labeled pediatric use(s)* • Statement of indicated use does not explicitly refer to pediatric patients *Study information* • Pediatric patients 6 to 16 yr were included in a clinical study (n = 11). • Pharmacokinetics, safety, and efficacy were similar to those in an adult population.
55. Immune globulin intravenous (human), 10% solution (Gammagard liquid) (125105) 04/27/2005	Treatment of primary immunodeficiency	*Labeled pediatric use(s)* • Statement of indicated use does not explicitly refer to pediatric patients • Safety and efficacy have not been established in patients <2 yr *Study information* • Pharmacokinetics, safety, and efficacy were evaluated in pediatric patients 5 to 16 yr (n = 15). • Results were similar to those seen in adults.
56. Immune globulin intravenous (human), 10% liquid (Privigen) (125201) 07/26/2007	• Primary humoral immunodeficiency (PI) • Chronic immune thrombocytopenic purpura (ITP)	*Labeled pediatric use(s)* • PI in patients ≥3 yr • ITP in patients ≥15 yr • Safety and effectiveness of Privigen have not been established in pediatric patients <3 yr with PI. • Safety and effectiveness of Privigen have not been established in pediatric patients <15 yr with chronic ITP. *Study information* • Safety and efficacy were assessed in pediatric patients with PI (n = 31). • Safety and efficacy profiles were comparable to those for adults. • Safety, efficacy, and tolerability were established in patients 15 to 69 yr with ITP.
57. Immune globulin subcutaneous (human) (Vivaglobin) (125115) 01/09/2006	Treatment of patients with primary humoral immunodeficiency	*Labeled pediatric use(s)* • Statement of indicated use does not explicitly refer to pediatric patients • Safety and efficacy in pediatric subjects <2 yr have not been established. *Study information* • Two studies enrolled pediatric patients 3 to 16 yr (n = 10, n = 22). • Safety and efficacy were similar to those seen in an adult population.
58. Immune globulin subcutaneous (human) (IGSC), 20% liquid (Hizentra) (125350) 03/04/2010	Treatment of primary immunodeficiency (PI)	*Labeled pediatric use(s)* • PI in patients 2 to 16 yr • Safety and efficacy in pediatric patients <2 yr have not been established. *Study information* • Safety and efficacy have been established in a U.S. study (n = 10) and a European study (n = 23). • Safety and efficacy profiles were similar to those for an adult population.

Generic Name (Trade Name) (BLA Number) Original Approval Date	Approved Indication(s)	Highlights of Pediatric Information in Labeling
59. Immune globulin intravenous (human), 5% liquid (Gammaplex) (125329) 09/17/2009	Primary humoral immunodeficiency	Safety and efficacy in a pediatric population have not been established. *Study information* • Six pediatric patients were included in a study but could not be evaluated separately because of small sample size.
60. IncobotulinumtoxinA (Xeomin) (125360) 07/30/2010	• Cervical dystonia • Blepharospasm	Safety and efficacy of incobotulinumtoxinA in patients <18 yr have not been approved.
61. Infliximab (Remicade) (103772) 08/24/1998	• Crohn's disease (CD) • Ulcerative colitis • Ankylosing spondylitis • Psoriatic arthritis • Plaque psoriasis	*Labeled pediatric use(s)* • CD in patients ≥6 yr • Use not established for patients <6 yr with CD • Long-term safety and efficacy in pediatric CD patients not determined • Use by pediatric patients with ulcerative colitis and plaque psoriasis not established *Study information* • Safety and efficacy have been assessed in patients 6 to 17 yr with CD (n = 112). • Findings showed that infliximab was effective at reducing CD signs and symptoms and maintaining clinical remission. • Safety and efficacy were assessed in patients 4 to 17 yr with juvenile rheumatoid arthritis (n = 60). • Study failed to establish efficacy of infliximab in patients with juvenile rheumatoid arthritis. • Findings showed high placebo response rate and higher rate of immunogenicity in pediatric patients than in adults. *Boxed warning* • Lymphoma and other malignancies, some fatal, have been reported in children and adolescent patients treated with tumor necrosis factor (TNF) blockers, of which infliximab is a member. • Postmarketing cases of hepatosplenic T-cell lymphoma have been reported in patients treated with TNF blockers, including infliximab. All cases were reported in patients with Crohn's disease and ulcerative colitis, the majority of whom were adolescent or young adult males.
62. Interferon alfacon-1 (Infergen) (103663) 10/06/1997	Chronic hepatitis C virus infection in patients ≥18 yr	Safety and effectiveness of interferon alfacon-1 in patients <18 yr have not been established. It is not recommended as therapy in pediatric patients.
63. Interferon beta-1A (Rebif) (103780) 03/07/2002	Relapsing forms of multiple sclerosis	Safety and effectiveness of interferon beta-1A in pediatric patients have not been studied.

Generic Name (Trade Name) (BLA Number) Original Approval Date	Approved Indication(s)	Highlights of Pediatric Information in Labeling
64. Interferon gamma-1B (Actimmune) Intermune Pharms (103836) 02/25/1999	• Reduction in infections in patients with chronic granulomatous disease (CGD) • Delaying disease progression of osteopetrosis	*Labeled pediatric use(s)* • CGD • Osteopetrosis • Statements of indicated uses do not explicitly refer to pediatric patients *Study information* • Safety and efficacy were assessed in patients 1 to 44 yr with CGD (*n* = 128). • A statistically significant benefit in time to serious infection was found in the interferon gamma-1B group compared with placebo group. • Safety and efficacy were assessed in patients 1 mo to 8 yr with osteopetrosis (*n* = 16). • Median time to disease progression was delayed in the group receiving interferon gamma-1B plus calcitriol vs. the group receiving calcitriol alone.
65. Laronidase (Aldurazyme) (125058) 04/30/2003	Hurler and Hurler-Scheie forms of mucopolysaccharidosis I (MPS I)	*Labeled pediatric use(s)* • Hurler and Hurler-Scheie forms of MPS I • No information in the label regarding use in a specific age group within the pediatric population *Study information* • Safety and efficacy were assessed in patients 6 to 43 yr (*n* = 45). • Improvement in breathing and walking capacities were found in the laronidase group compared with placebo group. • Safety and efficacy were assessed in patients 6 mo to 5 yr (*n* = 20). • Safety and efficacy findings were similar to those from a study that included both pediatric and adult populations. • Common adverse events included infusion reactions and otitis media.
66. Methoxy polyethylene glycol-epoetin beta (Mircera) (125164) 11/14/2007	Anemia associated with chronic renal failure	Safety and efficacy of Mircera in pediatric patients have not been established.
67. Natalizumab (Tysabri) (125104) 11/23/2004	• Relapsing forms of multiple sclerosis (MS) • Crohn's disease (CD)	Safety and effectiveness of Tysabri in pediatric patients <18 yr with MS or CD have not been established. Tysabri is not indicated for use by pediatric patients.
68. Ofatumumab (Arzerra) (125326) 10/26/2009	Chronic lymphocytic leukemia	Safety and effectiveness in pediatric patients have not been established.

Generic Name (Trade Name) (BLA Number) Original Approval Date	Approved Indication(s)	Highlights of Pediatric Information in Labeling
69. Omalizumab (Xolair) (103976) 06/20/2003	Moderate to severe asthma	*Labeled pediatric use(s)* • Moderate to severe persistent asthma in patients ≥12 yr • Not indicated for patients <12 yr *Study information* • Safety and effectiveness were assessed in two studies with asthma patients 6 to <12 yr (*n* = 926). • Exacerbations were reduced, but other efficacy measures did not differ from those for placebo group. • Known risk of anaphylaxis and malignancy in patients ≥12 yr outweighs benefit in children <12 yr.
70. Oprelvekin (Neumega) (103694) (11/25/1997)	Prevention of severe thrombocytopenia following myelosuppressive chemotherapy	A safe and effective dose of Neumega in pediatric patients has not been established. *Study information* • A dose-escalation study involving 43 pediatric patients did not reduce need for transfusions and projected the effective dose to be higher than the maximum tolerated pediatric dose. • Papilledema was a dose-limiting adverse effect.
71. Palifermin (Kepivance) (125103) 12/15/2004	Oral mucositis	Safety and effectiveness of Kepivance in pediatric patients have not been established.
72. Palivizumab (Synagis) (103770) 6/19/1998	Prevention of lower respiratory tract disease caused by respiratory syncytial virus (RSV) in pediatric patients	*Labeled pediatric use(s)* • Prevention of lower respiratory tract disease caused by RSV in pediatric patients *Study information* • Safety and efficacy were assessed in two studies with patients ≤24 mo (*n* = 2,789). • Findings showed a significant reduction in hospitalization for RSV infection in patients receiving palivizumab than those receiving placebo.
73. Panitumumab (Vectibix) (125147) 09/27/2006	Metastatic colorectal carcinoma	Pharmacokinetics, safety, and effectiveness in pediatric patients have not been established.
74. Pegfilgrastim (Neulasta) (125031) 01/31/2002	To decrease infections in patients receiving myelosuppressive anticancer drugs associated with febrile neutropenia	Safety and efficacy of Neulasta in pediatric patients have not been established. *Study information* • Pharmacokinetics and safety studies were conducted with 37 pediatric patients with sarcoma. • The most common adverse reaction was bone pain.

Generic Name (Trade Name) (BLA Number) Original Approval Date	Approved Indication(s)	Highlights of Pediatric Information in Labeling
75. Peginterferon alfa-2A (Pegasys) (103964) 10/16/2002	Chronic hepatitis C (CHC) in adults	*Labeled pediatric use(s)* • CHC in patients 5 yr and older with compensated liver disease not previously treated with interferon alpha and patients with histological evidence of cirrhosis and compensated liver disease was treated with Peginterferon alfa-2A. Peginterferon alfa-2A should be given in combination with Copegus unless contraindicated. Peginterferon alfa-2A contains benzyl alcohol, which has been associated with an increased incidence of neurological and other complications in neonates and infants. *Study information* • Information on safety, dosing, and efficacy from a randomized trial (114 subjects) comparing combination with monotherapy is available. • Pediatric subjects treated with Pegasys plus Copegus combination therapy showed delays in weight and height increases after 48 wk of therapy compared with those at baseline.
76. Peginterferon alfa-2A; ribavirin (Pegasys Copegus combination pack) (125083) 06/04/2004	Chronic hepatitis C	• See labeling information for Pegasys. • Labeling is not available for the combination pack.
77. Peginterferon alfa-2B (Pegintron) (103949) 01/19/2001	*Combination therapy* • In combination with ribavirin for chronic hepatitis C in patients ≥3 yr *Monotherapy* • Chronic hepatitis C in patients ≥18 yr	*Labeled pediatric use(s)* • In combination with ribavirin for chronic hepatitis C in patients ≥3 yr • Safety and effectiveness of peginterferon alfa-2B in combination with ribavirin in pediatric patients <3 yr have not been established. *Study information* • Safety and efficacy of peginterferon alfa-2B and ribavirin were established in patients 3 to 17 yr (n = 107).
78. Peginterferon alfa-2B; ribavirin (Pegintron/Rebetol combo pack) (125196) 06/13/2008	Chronic hepatitis C in patients ≥18 yr	Safety and efficacy in pediatric patients <18 yr have not been established. *Study information* • Pharmacokinetic evaluations for combination peginterferon alfa-2B and ribavirin have not been performed.
79. Pegloticase (Krystexxa) (125293) 09/14/2010	Chronic gout in adult patients	Safety and efficacy in pediatric patients <18 yr have not been established.
80. Protein C concentrate (human) (Ceprotin) (125234) 03/30/2007	Prevention and treatment of venous thrombosis and purpura fulminans (PF) in congenital protein C deficiency	*Labeled pediatric use(s)* • Recommended for neonate and pediatric use *Study information* • Several retrospective and prospective studies have evaluated safety and efficacy in neonates and pediatric patients. • A pivotal study assessed the efficacy of Ceprotin in treating PF and other thromboembolic events in patients 0 to 25 yr (n = 18). • When compared with a historical control group, Ceprotin was more effective than fresh frozen plasma or other conventional anticoagulants.

Generic Name (Trade Name) (BLA Number) Original Approval Date	Approved Indication(s)	Highlights of Pediatric Information in Labeling
81. Ranibizumab (Lucentis) (125156) 06/30/2006	• Macular degeneration • Macular edema	Safety and efficacy in pediatric patients have not been established.
82. Rasburicase (Elitek) (103946) 07/12/2002	Management of hyperuricemia in patients with leukemia, lymphoma, and solid tumor malignancies who are receiving anticancer therapy expected to result in tumor lysis and subsequent elevation of plasma uric acid	*Labeled pediatric use(s)* • Hyperuricemia in pediatric patients with malignancies who are receiving anticancer therapy expected to result in tumor lysis *Study information* • Safety and efficacy in patients 1 mo to 17 yr were studied (n = 246). • Children <2 yr had a lower rate of achieving normal uric acid concentrations than those 2 to 17 yr. • Incidence of renal failure was similar between the rasburicase and allopurinol groups.
83. Rho(D) immune globulin intravenous (human) (Rhophylac) (125070) 02/12/2004	• Suppression of Rhesus (Rh) isoimmunization in o Pregnancy and obstetric conditions o Incompatible transfusions in Rho (D)-negative individuals • Raising platelet counts in adults with idiopathic thrombocytopenic purpura	• Safety and effectiveness in pediatric subjects being treated for an incompatible transfusion have not been established. • The physician should weigh the potential risks against the benefits of Rhophylac, particularly in girls whose later pregnancies may be affected if Rh isoimmunization occurs.
84. Rilonacept (Arcalyst) (125249) 02/27/2008	Cryopyrin-associated periodic syndromes (CAPS)	*Labeled pediatric use(s)* • CAPS, including familial cold autoinflammatory syndrome and Muckle-Wells syndrome in patients ≥12 yr • Safety and efficacy in patients <12 yr have not been established. *Study information* • Pharmacokinetics, safety, and efficacy in patients 12 to 16 yr were assessed (n = 6). • Findings showed improvement in baseline symptom scores and in markers of inflammation. • It is unknown whether rilonacept will alter bone development in children.
85. Rimabotulinum-toxinB (Myobloc) (103846) 12/08/2000	Cervical dystonia	Safety and effectiveness in pediatric patients have not been established.
86. Rituximab (Rituxan) (103705) 11/26/1997	• Non-Hodgkin's lymphoma • Chronic lymphocytic leukemia • Rheumatoid arthritis • Wegener's granulomatosis and microscopic polyangiitis	• The safety and effectiveness of Rituxan in pediatric patients have not been established. • FDA has not required pediatric studies of patients 0 to 16 yr with polyarticular juvenile idiopathic arthritis because of concerns regarding the potential for prolonged immunosuppression.

Generic Name (Trade Name) (BLA Number) Original Approval Date	Approved Indication(s)	Highlights of Pediatric Information in Labeling
87. Romiplostim (Nplate) (125268) 08/22/2008	Chronic immune (idiopathic) thrombocytopenic purpura	Safety and effectiveness in pediatric patients <18 yr have not been established.
88. Sipuleucel T (Provenge) (125197) 04/29/2010	Metastatic hormone-refractory prostate cancer	No pediatric use section or other reference to children in label
89. Tenecteplase (Tnkase) (103909) 06/02/2000	Reduction in mortality associated with acute myocardial infarction	Safety and effectiveness in pediatric patients have not been established.
90. Thrombin, topical (human) (Evithrom) (125247) 8/27/2007	Aid to hemostasis during surgery	*Labeled pediatric use(s)* • Aid to hemostasis during surgery in pediatric patients *Study information* • Safety and efficacy were established in a clinical trial that included 8 pediatric patients 0 to 12 yr undergoing liver surgery.
91. Thrombin, topical (recombinant) (Recothrom) (125248) 1/17/2008	Aid to hemostasis during surgery	Safety and effectiveness in a pediatric population have not been fully established. *Study information* • Recothrom was evaluated in four pediatric patients 12 to 16 yr.
92. Tocilizumab (Actemra) (125276) 01/08/2010	• Rheumatoid arthritis • Systemic juvenile idiopathic arthritis (SJIA)	*Labeled pediatric use(s)* • SJIA • Safety and effectiveness in pediatric patients with conditions other than SJIA have not been established. *Study information* • Efficacy and safety in pediatric patients with SJIA were assessed (n = 75). • The response in the Actemra group was significant compared with that in the placebo group.
93. Tositumomab; iodine I 131 tositumomab (Bexxar) (125011) 06/27/2003	Non-Hodgkin's lymphoma	Safety and effectiveness of Bexxar in children have not been established.
94. Trastuzumab (Herceptin) Genentech (103792) 10/25/1998	• *HER2*-overexpressing breast cancer • *HER2*-overexpressing metastatic gastric or gastroesophageal junction adenocarcinoma	Safety and effectiveness of Herceptin in pediatric patients have not been established.
95. Ustekinumab (Stelara) (125261) 09/25/2009	Plaque psoriasis in adult patients	Safety and effectiveness of Stelara in pediatric patients have not been evaluated.

Generic Name (Trade Name) (BLA Number) Original Approval Date	Approved Indication(s)	Highlights of Pediatric Information in Labeling
96. Vaccinia immune globulin intravenous (Vigiv) (125109) 05/02/2005	• Eczema vaccinatum • Progressive vaccinia • Severe generalized vaccinia • Vaccinia virus infections in patients with skin conditions	Safety and effectiveness in the pediatric population have not been established.
97. von Willebrand factor/coagulation Factor VIII complex (human) (Wilate) (125251) 12/4/2009	Treatment of bleeding episodes in patients with von Willebrand disease (VWD)	*Labeled pediatric use(s)* • Statement of indicated use does not explicitly refer to pediatric patients *Study information* • Eleven pediatric patients between 5 and 16 yr with VWD (eight with type 3, one with type 2, two with type 1) were treated with Wilate for 234 bleeding episodes (BEs) in clinical studies. These studies showed that 88% of the Bes were successfully treated in this population. No dose adjustment is needed for pediatric patients, as administered dosages were similar to those used by the adult population.

TABLE D-2 Information on Pediatric Trials Registered at ClinicalTrials.gov for Biologics Approved by FDA after January 1, 1997 (products are listed *separately* for CDER- and CBER-regulated products)

Drug (CDER)	Condition	Ages of Trial Participants	Trial Phase
Biologics Under the Jurisdiction of the Center for Drug Evaluation and Research			
1. Abatacept	Juvenile rheumatoid arthritis	6 to 17 yr	III
(Orencia)	Type 1 diabetes mellitus	6 to 45 yr	II
(125118)	Acute graft-versus-host disease during transplant	>12 yr	II
12/23/2005	Wegener's granulomatosis	>15 yr	I/II
	Uveitis	>6 yr	II
2. AbobotulinumtoxinA	Spasticity in cerebral palsy	2 to 17 yr	III
(Dysport)	Idiopathic toe walking	5 to 15 yr	II
(125274)	Cerebral palsy	25 mo to 9 yr	IV
04/29/2009	Leg length inequality; foot deformities	6 to 16 yr	IV
	Torticollis	4 mo to 1 yr	I
	Lower limb length discrepancy	5 to 21 yr	III
	Myelomeningocele; neurogenic bladder	2 to 16 yr	IV
	Cerebral palsy	1 to 17 yr	I/II
	Muscle spasticity in cerebral palsy	3 to 12 yr	II
	Spastic diplegic cerebral palsy	3 to 18 yr	III
	Cerebral palsy	4 to 12 yr	I/II
	Spasticity	>2 yr	III
	Cerebral palsy; drooling	6 to 21 yr	n/s
	Cerebral palsy	5 to 15 yr	n/s
	Idiopathic clubfoot	1 day to 2 yr	n/s
	Spasticity in cerebral palsy	2 to 18 yr	IV
	Clubfoot	Up to 12 yr	n/s
	Stroke; brain injuries; spasticity	>12 yr	IV
	Spinal cord injury; pain	>15 yr	n/s
	Cerebral palsy	2 to 18 yr	I/II
	Spasticity, poststroke	>2 yr	n/s
	Hyperhidrosis	12 to 17 yr	IV
	Cerebral palsy	10 to 17 yr	II
	Esotropia	Up to 5 yr	n/s
	Hip pain in cerebral palsy	4 to 16 yr	II
	Cerebral palsy	8 to 11 yr	IV
3. Adalimumab	Juvenile rheumatoid arthritis	4 to 17 yr	III
(Humira)	Juvenile idiopathic arthritis	4 to 17 yr	III
(125057)	Plaque psoriasis	4 to 17 yr	III
12/31/2002	Juvenile idiopathic arthritis	4 to 17 yr	n/s
	Juvenile idiopathic arthritis	2 to 4 yr	III
	Enthesitis-related arthritis (ERA)	6 to 17 yr	III
	Focal glomerulosclerosis	2 to 40 yr	I
	Focal segmental glomerulosclerosis	1 to 50 yr	II
	Uveitis; juvenile arthritis	>4 yr	II/III
	Crohn's disease	6 to 17 yr	III
	Crohn's disease	15 to 75 yr	II/III
	Intestinal Behcet's disease	>15 yr	III
	Ankylosing spondylitis	>15 yr	III
	Ulcerative colitis	>15 yr	III
	Crohn's disease	7 to 18 yr	III
	Crohn's disease	15 to 75 yr	II/III
	Crohn's disease-like inflammatory bowel disease in chronic granulomatous disease	>10 yr	I/II
4. Agalsidase beta	Fabry disease	7 to 15 yr	II
(Fabrazyme)	Fabry disease	Infants	IV
(103979)	Fabry disease	5 to 85 yr	IV
04/24/2003	Fabry disease	5 to 18 yr	III

Biologics Under the Jurisdiction of the Center for Drug Evaluation and Research			
Drug (CDER)	Condition	Ages of Trial Participants	Trial Phase
	Fabry disease	>15 yr	IV
	Fabry disease	8 to 18 yr	n/s
	Fabry disease; proteinuria	14 to 95 yr	n/s
5. Alefacept (Amevive) (125036) 1/30/2003	Hematopoietic stem cell transplant	Up to 21 yr	n/s
	Type 1 diabetes mellitus	12 to 35 yr	II
	Psoriasis	12 to 17 yr	II
	Graft-versus-host disease	14 to 75 yr	III
	Resistant chronic graft-versus-host disease	Up to 70 yr	I/II
6. Alemtuzumab (Campath) (103948) 05/07/2001	In association with stem cell transplants for various hematologic malignancies, multiple trials	Various age ranges across pediatric population	0, I, II, III
	Acute lymphoblastic leukemia	Up to 30 yr	II
	Aplastic anemia	≥2	II
	Chronic lymphocytic leukemia	Up to 69 yr	II
7. Alglucosidase alfa (Lumizyme) (125291) 05/24/2010	Pompe disease (late onset)	>8 yr	III
	Pompe disease (late onset)	>1 yr	n/s
	Pompe disease (infantile onset)	Up to 26 wk	II/III
	Pompe disease (infantile onset)	6 to 36 mo	I/II
	Pompe disease	>1 mo	IV
8. Alglucosidase alfa (Myozyme) (125141) 04/28/2006	Pompe disease	<18 yr	IV
	Pompe disease (late onset)	8 to 18 yr	IV
	Pompe disease	>6 mo	IV
	Pompe disease	Up to 24 mo	IV
	Pompe disease (infantile onset)	<12 mo	n/s
	Pompe disease	>8 yr	n/s
	Pompe disease (late onset)	>8 yr	IV
9. Anakinra (Kineret) (103950) 11/14/2001	Type 1 diabetes mellitus	6 to 18 yr	I/II
	Atopic dermatitis	10 to 18 yr	I
	Juvenile chronic arthritis	2 to 17 yr	II
	Juvenile idiopathic arthritis	2 to 20 yr	II/III
	Neonatal-onset multisystem inflammatory disease	Neonates	
	Relapsing polychondritis	12 to 15 yr	II
10. Basiliximab (Simulect) (103764) 05/12/1998	Liver transplantation complications	Up to 16 yr	IV
	Kidney transplantation complications	Up to 20 yr	n/s
	Noninfectious uveitis	12 to 80 yr	II
	Kidney transplantation complications	1 to 18 yr	III
11. Becaplermin (Regranex) (103691) 12/16/1997	*None*		
12. Bevacizumab (Avastin) (125085) 02/26/2004	Solid tumors	Up to 21 yr	I
	Glial cell tumors	3 to 21 yr	II
	Central nervous system tumors	18 mo to 23 yr	I
	Intrinsic pontine glioma	3 to 18 yr	II
	Central nervous system tumors	1 to 25 yr	n/s
	Pulmonary vein stenosis	No age range given; infants and children	n/s
	Brain cancer	Up to 21 yr	II
	Gliomas	3 to 30 yr	n/s
	Central nervous system tumors	3 to 21 yr	II/III
	Neuroblastoma	Up to 30 yr	I
	Refractory solid tumors	12 mo to 20 yr	I
	Medullablastoma	Up to 19 yr	II
	Central nervous system tumors	Up to 21 yr	II
	Sarcoma	Up to 29 yr	II

Biologics Under the Jurisdiction of the Center for Drug Evaluation and Research			
Drug (CDER)	Condition	Ages of Trial Participants	Trial Phase
	Osteosarcoma	Up to 30 yr	III
	Solid tumor	1 to 30 yr	I/II
	Central nervous system tumors	Up to 21 yr	II
	Refractory solid tumors; leukemia	Up to 21 yr	I
	Sarcoma	6 mo to 18 yr	II
	Retinopathy of prematurity	30 wk and older	n/s
	Neurofibromatosis type 2	≥12 yr	II
	Retinopathy of prematurity	30 to 36 wk	I
	Sarcoma	1 to 29 yr	II
	Refractory solid tumors	1 to 21 yr	I
	Retinopathy of prematurity	Up to 22 wk	II
	Retinopathy of prematurity	30 to 36 wk	II
	Retinopathy of prematurity	1 to 12 mo	II/III
	Central nervous system tumors	≥15 yr	I
	Sarcoma	≥13 yr	II
	Neovascular glaucoma	14 to 72 yr	II
	Sarcoma	1 to 29 yr	n/s
	Neovascular glaucoma	10 to 80 yr	n/s
	Glioma	3 to 18 yr	II
	Gastrointestinal cancer	≥18 mo	II
	Germ cell tumors	12 to 65 yr	II
	Neuroblastoma	≥1 yr	I
13. Canakinumab (Ilaris) (125319) 06/17/2009	Cryopyrin-associated periodic syndromes	≥2 yr Up to 4 yr ≥3 yr 4 to 75 yr	III (all)
	Systemic juvenile arthritis	≥2 yr 2 to 19 yr	III (all)
	Type 1 diabetes mellitus	6 to 45 yr 6 to 35 yr	II
	Familial Mediterranean fever	4 to 20 yr 12 to 75 yr	II
	Neonatal-onset multisystem inflammatory disease	2 to 25 yr	III
	Mevalonate kinase deficiency	≥2 yr	II
	NALP3 mutation	4 to 75 yr	II
	Tumor necrosis factor receptor-associated periodic syndromes	≥4 yr	II
14. Certolizumab pegol (Cimzia) (125160) 04/22/2008	Crohn's disease	6 to 65 yr	II (all)
	Plaque psoriasis	Up to 18 yr	II
15. Cetuximab (Erbitux) (125084) 02/12/2004	Brain cancer	3 to 21 yr	II
	Refractory solid tumors	1 to 18 yr	I
16. Collagenase *Clostridium histolyticum* (Xiaflex) (125338) 02/02/2010	*None*		
17. Daclizumab (Zenapax) (103749) 12/10/1997	Immune suppression in kidney transplantation	Up to 21 yr	
	Cardiac transplantation complications	1 mo to 18 yr	I/II
	Cardiac transplantation complications	Up to 21 yr	n/s
	Juvenile idiopathic arthritis-associated uveitis	6 to 18 yr	II
	Type I diabetes mellitus	8 to 45 yr	III
	Type I diabetes mellitus	2 to 40 yr	II

Biologics Under the Jurisdiction of the Center for Drug Evaluation and Research			
Drug (CDER)	Condition	Ages of Trial Participants	Trial Phase
	Leukemia	≥10 yr	II
	Anemia	≥2 yr	II
	Ulcerative colitis	≥12 yr	II
	Cardiac transplantation complications	≥13 yr	IV
	Cystinosis	≥7 yr	n/s
	Uveitis	≥6 yr	n/s
	Uveitis	≥13 yr	IV
18. Darbepoetin alfa (Aranesp) (103951) 09/17/2001	Anemia due to chronic renal failure	Up to 17 yr	III
	Anemia of prematurity	Up to 49 h	II
	Anemia due to chronic kidney disease	1 to 18 yr	III
19. Denileukin diftitox (Ontak) (103767) 02/05/1999	Anaplastic large-cell lymphoma	2 to 24 yr	II
	Graft-versus-host disease	≥2 yr	II
	Neuroblastoma	Up to 21 yr	II
	Neuroblastoma	Up to 21 yr	I
	Graft-versus-host disease	≥6 yr	II
	Refractory lymphoid malignancies	Any age	II
	Leukemia	≥2 yr	II
20. Denosumab (Prolia/Xgeva) (125320) 06/01/2010	Giant-cell tumor of bone	≥12 yr	II
21. Ecallantide (Kalbitor) (125277) 11/27/2009	Hereditary angioedema	≥10 yr	n/s
	Hereditary angioedema	≥10 yr	III
	Hereditary angioedema	2 to 17 yr	II/III
	Hereditary angioedema	≥10 yr	III
22. Eculizumab (Soliris) (125166) 03/16/2007	Hemoglobinuria	2 to 17 yr	I/II
	Atypical hemolytic-uremic syndrome	12 to 18 yr	II
	Atypical hemolytic-uremic syndrome	12 to 18 yr	II
	Hemoglobinuria	≥12 yr	II
	Hemoglobinuria	≥12 yr	II
	Shiga toxin hemolytic-uremic syndrome	≥2 mo	II/III
	Atypical hemolytic-uremic syndrome	1 mo to 18 yr	II
	Hemolytic-uremic syndrome	≥2 yr	n/s
23. Etanercept (Enbrel) (103795) 11/02/1998	Polyarticular juvenile idiopathic arthritis	≥2 mo	IV
	Fanconi anemia	≥4 yr	n/s
	Kawasaki disease	2 mo to 20 yr	II
	Psoriasis	4 to 17 yr	n/s
	Psoriasis	4 to 17 yr	III
	Idiopathic pneumonia syndrome after stem cell transplant	1 to 17 yr	II
	Histiocytosis	Up to 65 yr	II
	Type 1 diabetes mellitus	3 to 18 yr	I/II
	Graft-versus-host disease, multiple trials	Various age ranges across pediatric population	II, III
	Dermatomyositis	4 to 16 yr	II/III
	Idiopathic pneumonia syndrome after stem cell transplant	≥6 yr	II
	Wegener's granulomatosis	10 to 70 yr	II
	Psoriasis	n/s	III
	Leukemia	2 to 18 yr	III
	Uveitis	Any age	II

Biologics Under the Jurisdiction of the Center for Drug Evaluation and Research			
Drug (CDER)	Condition	Ages of Trial Participants	Trial Phase
24. Galsulfase (Naglazyme) (125117) 05/31/2005	Mucopolysaccharidosis VI, multiple trials	Various age ranges	I, II, III, IV
25. Golimumab (Simponi) (125289) 04/24/2009	Juvenile idiopathic arthritis	2 to 18 yr	III
26. Ibritumomab tiuxetan (Zevalin) (125019) 02/19/2002	Lymphoma Non-Hodgkin's lymphoma	Up to 21 yr Up to 64 yr	I II
27. Idursulfase (Elaprase) (125151) 07/24/2006	Hunter syndrome Hunter syndrome Mucopolysaccharidosis II Hunter syndrome Mucopolysaccharidosis II	≥5 yr ≥5 yr 5 to 25 yr 3 to 18 yr 6 to 35 yr	n/s II/III II/III n/s II/III
28. IncobotulinumtoxinA (Xeomin) (125360) 07/30/2010	*None*		
29. Infliximab (Remicade) (103772) 08/24/1998	Juvenile rheumatoid arthritis Ulcerative colitis Ulcerative colitis Graft-versus-host disease Graft-versus-host disease Kawasaki disease Kawasaki disease Uveitis Juvenile idiopathic arthritis Juvenile idiopathic arthritis Juvenile idiopathic arthritis Spondylarthropathies Crohn's disease Chronic granulomatous disease Uveitis	4 to 18 yr 6 to 18 yr 6 to 17 yr 6 mo to 75 yr Up to 18 yr Up to 18 yr Up to 17 yr Up to 18 yr 4 to 15 yr 1 to 16 yr 4 to 18 yr Up to 18 yr 6 to 17 yr ≥10 yr ≥9 yr	II n/s III II I I III IV III n/s III II/III III I/II n/s
30. Interferon alfacon-1 (Infergen) (103663) 10/06/1997	*None*		
31. Interferon beta-1A (Rebif) (103780) 03/07/2002	Clinically isolated syndrome	18 mo to 65 yr	III
32. Interferon gamma-1B (Actimmune) (103836) 02/25/1999	Osteopetrosis Chronic granulomatous disease HIV infection Lymphoma Leukocyte adhesion deficiency syndrome Pulmonary tuberculosis Nontuberculosis mycobacterial infections Cystic fibrosis Fungal infections Cryptococcal meningitis Chronic granulomatous disease	2 mo to 10 yr All ages 1 to 17 yr Up to 20 yr Children, not specified ≥5 yr ≥5 yr ≥12 yr ≥2 yr ≥13 yr Any age	III IV I II/III II II II I/II II II IV

Biologics Under the Jurisdiction of the Center for Drug Evaluation and Research			
Drug (CDER)	Condition	Ages of Trial Participants	Trial Phase
33. Laronidase (Aldurazyme) (125058) 04/30/2003	Mucopolysaccharidosis I, multiple studies	All ages	I, II, III, IV
34. Methoxy polyethylene glycol-epoetin beta (Mircera) (125164) 11/14/2007	Anemia	5 to 17 yr	II
	Low birth weight	Up to 3 days	n/s
	Cerebral malaria	6 mo to 15 yr	II/III
	Lymphoproliferative disorders	18 mo and older	
35. Natalizumab (Tysabri) (125104) 11/23/2004	Crohn's disease	12 to 17 yr	II
36. Ofatumumab (Arzerra) (125326) 10/26/2009	Leukemia	All ages	II
37. Omalizumab (Xolair) (103976) 06/20/2003	Asthma, multiple trials for moderate or severe asthma	≥ 6 yr or ≥12 yr	III, IV
	Milk allergy	4 to 18 yr	n/s
	Eosinophilic esophagitis	12 to 60 yr	n/s
		12 to 76 yr	I
	Lung disease	≥12 yr	IV
	Urticaria	12 to 75 yr	II
		12 to 75 yr	III
		12 to 75 yr	III
		12 to 75 yr	III
	Cystic fibrosis	≥12 yr	IV
	Hyper-immunoglobulin E syndrome	6 to 76 yr	I
	Gastroenteritis	12 to 76 yr	II
	Peanut allergy	6 to 75 yr	II
		6 to 75 yr	II
		≥12 yr	I/II
	Atopic dermatitis	12 to 60 yr	IV
38. Oprelvekin (Neumega) (103694) (11/25/1997)	Stem cell transplantation in malignancies	All ages	II
	Solid tumors	Up to 45 yr	I
39. Palifermin (Kepivance) (125103) 12/15/2004	Mucositis	1 to 16 yr	II
	Mucositis	2 to 18 yr	I
	Leukemia	1 to 16 yr	I
	Severe combined immunodeficiency	2 to 20 yr	I/II
	Acute myeloid leukemia; advanced myelodysplastic syndromes	Up to 65 yr	II
	Lymphoma	12 to 65 yr	I
	Graft-versus-host disease	3 to 65 yr	I/II
	Mucositis	12 to 65 yr	II
	Graft-versus-host disease	3 to 65 yr	I/II
	Lymphoma	12 to 70 yr	II
	Epidermolysis bullosa	Up to 21 yr	0
	Severe combined immunodeficiency	18 mo to 20 yr	I
40. Palivizumab (Synagis) (103770) 6/19/1998	Respiratory syncytial virus infection	Up to 2 yr	
	Unhealthy children with a history of prematurity	5 to 6 mo	II
	Airway hyperreactivity	3 to 6 yr	
	Chronic lung disease	Up to 24 mo	IV
	Healthy, previously dosed children	Up to 24 mo	I/II
	Heart disease	Up to 24 mo	III
	Pain from palivizumab injection	1 mo to 2 yr	IV

Biologics Under the Jurisdiction of the Center for Drug Evaluation and Research			
Drug (CDER)	Condition	Ages of Trial Participants	Trial Phase
	Recurrent wheezing	3 mo to 1 yr	n/s
41. Panitumumab (Vectibix) (125147) 09/27/2006	Solid tumors	1 to 17 yr	I
42. Pegfilgrastim (Neulasta) (125031) 01/31/2002	Solid malignancies	Up to 18 yr	II
	Solid malignancies	Up to 18 yr	II
	Type 1 diabetes	12 to 45 yr	I/II
	Sarcoma	Up to 21 yr	II
43. Peginterferon alfa-2A (Pegasys) (103964) 10/16/2002	Hepatitis B	3 to 17 yr	III
	Hepatitis C	5 to 18 yr	III
	Hepatitis C; hemophilia	≥12 yr	IV
	Hepatitis C; thalassemia	≥12 yr	IV
	Polycythemia vera or essential thrombothycemia	≥18 wk	II
	Hepatitis C	15 to 65 yr	III
44. Peginterferon alfa-2A; ribavirin (Pegasys Copegus combination) (125083) 06/04/2004	Hepatitis C	5 to 18 yr	III
	Hepatitis C	>12 yr	IV
45. Peginterferon alfa-2B (Pegintron) (103949) 01/19/2001	Neurofibromatosis	18 mo to 21 yr	II
	Malignant melanoma	Up to 21 yr	II
	Sarcoma	5 to 40 yr	III
	HIV infection	3 mo to 16 yr	I
	Plexiform neurofibroma	1 to 21 yr	I
	Plexiform neurofibroma	18 mo to 21 yr	II
	Neurofibromatosis	2 to 30 yr	II
	Chronic myeloid leukemia	≥12 yr	I
	Hepatitis C	3 to 24 yr	III
	HIV infection	≥15 yr	II
	Glioma	Up to 21 yr	II
46. Peginterferon alfa-2B; ribavirin (Pegintron/Rebetol combo pack) (125196) 06/13/2008	Hepatitis C	3 to 17 yr	III
47. Pegloticase (Krystexxa) (125293) 09/14/2010	*None*		
48. Ranibizumab (Lucentis) (125156) 06/30/2006	*None*		
49. Rasburicase (Elitek) (103946) 07/12/2002	Hyperuricemia	Up to 18 yr	IV
	Leukemia; lymphoma	1 to 29 yr	II
	Malignancy-induced hyperuricemia	Age not specified	IV
	Tumor lysis syndrome	Up to 18 yr	IV
	Tumor lysis syndrome	≥2 yr	n/s
	Nutritional and metabolic diseases	Up to 18 yr	II
	Leukemia; lymphoma	≥15 yr	III
	Hyperuricemia	1 to 75 yr	III
	Mature B-cell lymphoma	Up to 20 yr	II/III
50. Rilonacept (Arcalyst)	Juvenile idiopathic arthritis	18 mo to 19 yr	II
	Familial Mediterranean fever	≥4 yr	II

Biologics Under the Jurisdiction of the Center for Drug Evaluation and Research			
Drug (CDER)	Condition	Ages of Trial Participants	Trial Phase
(125249) 02/27/2008	Cryopyrin-associated periodic syndromes	≥7 yr	III
51. RimabotulinumtoxinB (Myobloc) (103846) 12/08/2000	Cerebral palsy	2 to 18 yr	I/II
52. Rituximab (Rituxan) (103705) 11/26/1997	Leukemia; lymphoma Lymphoproliferative disorder	Six trials specifically include young patients; others include patients of any age	
	Neuroblastoma	6 mo to 21 yr 2 mo to 18 yr	n/s
	Hemophilia	≥18 mo	II
	Thrombotic thrombocytopenic purpura	≥12 yr >12 yr ≥12 yr	III II/II II
	Focal segmental glomerulosclerosis	5 to 60 yr 2 to 80 yr	II
	Transplant-related complications, multiple trials	Various age ranges across pediatric population	II, III, IV
	Type 1 diabetes mellitus	8 to 45 yr 8 to 45 yr	II/III IV
	Myositis	≥5 yr	II
	Immunoglobulin A nephropathy	≥5 yr	IV
	Nephrotic syndrome	2 to 18 yr	II/III
	Wegener's granulomatosis	≥15 yr	II/III
	Aplastic anemia	≥12 mo ≥2 yr	n/s II
	Neuromyelitis optica	12 to 86 yr	I
	Central nervous system tumor	18 mo to 75 yr	II
	Opsoclonus-myoclonus syndrome	6 mo to 19 yr	I/II
	Chronic focal encephalitis	5 to 25 yr	I
	Systemic lupus erythematosus	15 to 40 yr	II
	Lymphomatoid granulomatosis	≥12 yr	n/s
53. Romiplostim (Nplate) (125268) 08/22/2008	Idiopathic thrombocytopenic purpura Idiopathic thrombocytopenic purpura Idiopathic thrombocytopenic purpura Idiopathic thrombocytopenic purpura	12 mo to 17 yr 12 mo to 17 yr 1 to 18 yr ≥1 yr	III I/II III III
54. Tenecteplase (Tnkase) (103909) 06/02/2000	Restoration of function in dysfunctional central venous catheters	n/s	III
55. Tocilizumab (Actemra) (125276) 01/08/2010	Systemic juvenile idiopathic arthritis Relapsing polychondritis	Up to 19 yr 12 to 15 yr	 II
56. Tositumomab; iodine I 131 tositumomab (Bexxar) (125011) 06/27/2003	*None*		

Biologics Under the Jurisdiction of the Center for Drug Evaluation and Research			
Drug (CDER)	Condition	Ages of Trial Participants	Trial Phase
57. Trastuzumab (Herceptin) (103792) 10/25/1998	Osteosarcoma	<30 yr	II
	Recurrent osteosarcoma	Any age	II
58. Ustekinumab (Stelara) (125261) 09/25/2009	Psoriasis	12 to 18 yr	III

Biologics Under the Jurisdiction of the Center for Biologics Evaluation and Research			
Drug (CBER)	Condition	Ages of Trial Participants	Trial Phase
1. Albumin (human) (Albumin) (125154) 10/17/2006	Cardiac surgery	2 to 12 yr	IV
	Cirrhosis	12 to 75 yr	n/s
	Cardiac surgery	Up to 36 mo	n/s
2. Alpha1-proteinase inhibitor (human) (Aralast NP) (125039) 05/04/2007	Type 1 diabetes mellitus	8 to 35 yr	II
	Type 1 diabetes mellitus	8 to 35 yr	II
	Type 1 diabetes mellitus	6 to 45 yr	I
3. Alpha1-proteinase inhibitor (human) (Glassia) (125325) 07/01/2010	Type 1 diabetes mellitus	10 to 25 yr	I/II
4. Alpha1-proteinase inhibitor (human) (Zemaira) (125078) 07/08/2003	*None*		
5. Antihemophilic factor (recombinant), plasma/albumin free method (Advate) (125063) 07/25/2003 6. Antihemophilic factor (recombinant) (ReFacto) (103779) 03/06/2000 7. Antihemophilic factor (recombinant), plasma/albumin free (Xyntha) (125264) 02/21/2008	Hemophilia A (multiple studies)	Age ranges vary for specific studies but collectively cover the pediatric age range	I, II, III, IV
8. Antithrombin (recombinant) (ATryn) (125284) 02/06/2009	Postoperative hemorrhage	Up to 30 days	I
9. Anti-thymocyte globulin (rabbit) (thymoglobulin) (103869)	Transplant-related complications, multiple trials	Various age ranges across pediatric population	I, II, III, IV
	Type 1 diabetes mellitus	12 to 45 yr	I, II

Biologics Under the Jurisdiction of the Center for Drug Evaluation and Research			
Drug (CDER)	Condition	Ages of Trial Participants	Trial Phase
12/30/1998		12 to 35 yr	II
	Aplastic anemia	≥2 yr	II
		≥12 yr	II
		≥15 yr	II
	Systemic sclerosis	Up to 64 yr	II
	Myelodysplastic syndrome	All ages	II
	Toxicities of total body irradiation	Up to 21 yr	IV
10. Autologous cultured chondrocytes (Carticel) (103661) 08/22/1997	*None*		
11. Botulism immune globulin intravenous (human) (BabyBIG) (125034) 10/23/2003	Infant botulism	Up to 1 yr	n/s
12. C1 esterase inhibitor (human) (Berinert) (125287) 10/09/2009	Hereditary angioedema	≥6 yr	II/III
13. C1 esterase inhibitor (Cinryze) (125267) 10/10/2008	Hereditary angioedema	2 to 11 yr	II
	Hereditary angioedema	≥6 yr	II
14. Coagulation Factor VIIa (recombinant) (NovoSeven) (103665) 03/25/1999	Hemophilia A	Up to 8 yr	II
	Cardiopulmonary bypass	Up to 30 days	n/s
	Hemophilia A	≥2 yr	n/s
	Hemophilia	Up to 20 yr	IV
	Hemophilia A, B	≥2 yr	II
	Hemophilia A, B	≥2 yr	n/s
	Factor VII deficiency	Up to 90 yr	n/s
15. Coagulation Factor IX (recombinant) (Benefix) (103677) 02/01/1997	Hemophilia	All ages	
16. Crotalidae polyvalent immune Fab (ovine) (CroFab) (103788) 10/02/2000	Snakebite	2 to 80 yr	III
	Snakebite	≥1 yr	IV
17. Digoxin immune Fab (ovine) (DigiFab) (103910) 08/31/2001	*None*		
18. Fibrin sealant (human) (Artiss) (125266) 03/21/2008	*None*		
19. Fibrin sealant (human) (Evicel) (125010) 03/21/2003	Surgical blood loss	n/s	III

Biologics Under the Jurisdiction of the Center for Drug Evaluation and Research			
Drug (CDER)	Condition	Ages of Trial Participants	Trial Phase
20. Fibrin sealant (TachoSil) (125351) (04/02/2010)	Local bleeding, liver surgery Local bleeding, liver surgery	Up to 6 yr All ages	II/III III
21. Fibrin sealant (Tisseel) Baxter (103980) 05/01/1998	Burns Burns	≥6 yr Up to 65 yr	I/II III
22. Fibrinogen concentrate (human) (RiaSTAP) (125317) 01/16/2009	Cardiac surgical procedures Fibrinogen deficiency	Up to 18 yr ≥6 yr	II II
23. Hepatitis B immune globulin intravenous (human) (HepaGam B) (125237) 04/06/2007	*None*[a]		
24. Hepatitis B immune globulin (human) (Nabi-HB) (103945) 10/23/2001			
25. Immune globulin intravenous (human) (Flebogamma 5% DIF [dual inactivation plus nanofiltration]) (125077) 12/15/2003	Trials for infections (both bacterial and viral); pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections; neonatal infection; recurrent infections and immunoglobulin G subclass deficiency; HIV infection; Rasmussen encephalitis	Various age ranges across the pediatric age spectrum	I, II, III, IV
26. Immune globulin intravenous (human) 10% solution (Gammagard liquid) (125105) 04/27/2005	Multiple trials for primary immunodeficiencies Trials for transplantation-related complications Other trials for abnormal muscle movement in neuroblastoma; sickle cell pain crisis; hyperbilirubinemia; idiopathic thrombocytopenic purpura; postpolio syndrome		
27. Immune globulin intravenous (human) 5% liquid (Gammaplex) (125329) 09/17/2009			
28. Immune globulin injection (human) 10% caprylate/chromatography purified (Gamunex-C) (125046) 08/27/2003			
29. Immune globulin subcutaneous (human) (IGSC) 20% liquid (Hizentra) (125350) 03/04/2010			
30. Immune globulin intravenous (human) 5%			

Biologics Under the Jurisdiction of the Center for Drug Evaluation and Research			
Drug (CDER)	Condition	Ages of Trial Participants	Trial Phase
liquid (Octagam) (125062) 05/21/2004			
31. Immune globulin intravenous (human) 10% liquid (Privigen) (125201) 07/26/2007			
32. Immune globulin subcutaneous (human) (Vivaglobin) (125115) 01/09/2006			
33. Protein C concentrate (human) (Ceprotin) (125234) 03/30/2007	Protein C deficiency Protein C deficiency	≤6 mo n/s	II/III IV
34. Rho(D) immune globulin intravenous (human) (Rhophylac) (125070) 02/12/2004	*None*		
35. Sipuleucel T (Provenge) (125197) 04/29/2010	*None*		
36. Thrombin, topical (human) (Evithrom, a component of Evicel) (125247) 8/27/2007	Aid to hemostasis during surgery	Up to 17 yr	
37. Thrombin, topical (recombinant) (Recothrom) (125248) 1/17/2008			
38. Vaccinia immune globulin intravenous (Vigiv) (125109) 05/02/2005	Corneal scarring associated with vaccinia complication Prevention of vaccinal infection	≥1 yr n/s	II I
39. von Willebrand factor/coagulation Factor VIII complex (human) (Wilate) (125251) 12/4/2009	Bleeding prevention in surgery Hemophilia A Von Willebrand disease Hemophilia A	≥6 yr Any age n/s Any age	III n/s n/s n/s

[a] For the hepatitis B immune globulin products, none of the pediatric study listings involving this type of product cited either brand name.

NOTES: *For age*, n/s indicates a study for which the trial description did not state age explicitly but included children's hospital sites or had inclusion criteria or other information text that indicated the inclusion of pediatric patients (e.g., references to trial patients <10 kg). *For trial phase*, n/s indicates that the phase was not specified in the description. Search terms included a combination of the generic "biologic name AND children" or the "trade name AND children" to capture all studies that used that agent, whether

it was approved or still investigational. Some biologic agents that are often treated as interchangeable have been grouped together by their generic name when more than one is available and brand names are not noted. For a separately listed product that has relevant studies for the class of drug, at least one study identifies that brand name. Listing is not exhaustive of trials for same condition, age group, and phase.

E
Written Requests for Studies of Pediatric Hypertension: Longitudinal Changes in FDA Specifications

Jennifer Li[*]

The analysis presented here examines written requests for clinical studies issued by the Food and Drug Administration (FDA) to investigate potential drug treatments for pediatric hypertension. It begins with a summary of key elements in the written requests issued in the first 30 months after pediatric exclusivity provisions became effective in July 1998. The subsequent summaries describe key elements that either modified specifications (e.g., by more precisely describing safety follow-up) or added to them (e.g., by creating requirements for interim analyses). Some changes were required by legislation (e.g., registration of trials at ClinicalTrials.gov or documentation of a failed attempt to develop a new formulation).

FDA began with a basic template for the written requests for clinical studies to investigate drug treatments for pediatric hypertension. In general, the changes in elements of the template for both new and amended requests tended to have a few common purposes. They might

- add precision (e.g., by specifying a 1-year period for safety follow-up or by specifying minimum percentages of individuals of particular age or racial subgroups enrolled in trials);
- require more rigor in trial designs (e.g., by dropping the option for a trial with no placebo and only alternative doses of the test drug or by increasing the statistical power of trials to detect a clinically meaningful effect);
- require more accommodation of the developmental variability of children (e.g., by requiring sponsors to try to develop age-appropriate formulations, if needed); or
- increase transparency (e.g., by requiring that sponsors submit New Drug Application supplements to add to the label information—whether negative or positive—from clinical trials).

[*] Jennifer Li, M.D., is a member of the study committee.

KEY ELEMENTS SPECIFIED IN WRITTEN REQUESTS/AMENDMENTS ISSUED FROM 1998 TO 2000

- **Requested trials:**
    - Dose-ranging trial with hypertensive pediatric patients
    - Trial of pharmacokinetics (PKs) in children in four pediatric age groups (infants and toddlers, preschool-age children, school-age children, and adolescents)
    - Safety data from a controlled trial with an open treatment phase following the trial or from some other comparable database with a summary of all available information on the safety of the drug in pediatric patients

- **Race:** Ensure a mixture of black and nonblack patients
- **Formulation:** If no suspension/solution is available, a solid dosage form suspended in food could be used, if it has been shown to have acceptable bioavailability in adults
- **Trial design:** Randomized, double-blinded observation of parallel dose groups (it need not be successful, but it must be interpretable)
- **Four design options:** A, B, C, and D (Figure E-1)
    - *Trial Design A:* Each patient is randomized to placebo or to one of three doses ranging from slightly less than the lowest approved adult dose to slightly greater than the highest approved adult dose. After 2 weeks of treatment, the trial would be analyzed by looking for a significantly positive slope of the placebo-corrected change in blood pressure from baseline as a function of dose. If the slope of this line is not differentiable from 0, the trial would be unsuccessful but it would be interpretable.
    - *Trial Design B:* Design B is similar to Design A, but without a placebo arm. If analysis revealed a significantly positive slope to the dose-response line, the trial would be successful. If, however, no dose-response is detected, the trial will be considered not interpretable and not responsive to the written request.
    - *Trial Design C:* To avoid the possibility of uninterpretable findings, Design C consists of Design B modified to include a randomized withdrawal phase. Patients would be recruited and treated like those in the trial with Design B. At the end of a 2-week treatment period, patients would be rerandomized in a blinded fashion to continue to their assigned treatments or be withdrawn to placebo. A slope analysis would be used for the first phase and then, if the dose-response curve is flat, an analysis of the second phase would determine whether a blood pressure effect existed. The result would be considered interpretable no matter what the outcome, so long as the sample size for the withdrawal phase was adequate.
    - *Trial D:* Trial D uses randomized withdrawal. Patients would be force-titrated to maximal tolerated doses and then randomly withdrawn to lower doses, including placebo.

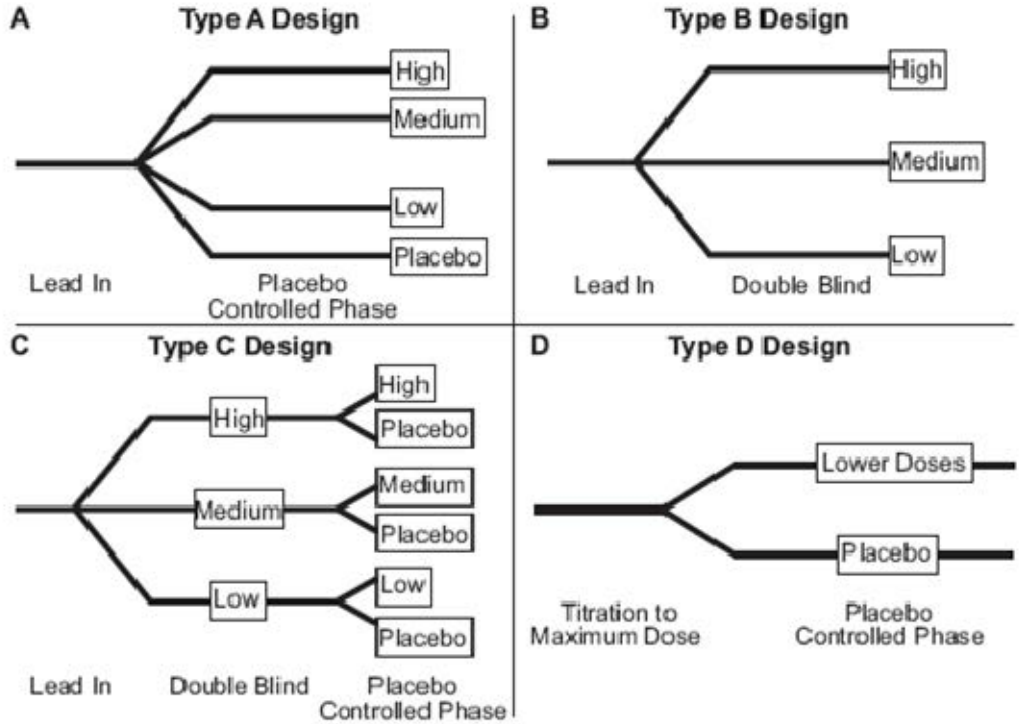

FIGURE E-1 Trial design options for pediatric hypertension trials provided for by FDA written requests. High, medium, and low refer to dose levels.
SOURCE: Reproduced with permission from Smith et al., 2008. Safety of placebo controls in pediatric hypertension trials, *Hypertension* 51(4):829–833.

- **Ages:** Adolescents and at least 50 percent of subjects 6 to 12 years of age or ≤Tanner 3
- **Statistical considerations:** 80 percent power to detect a treatment effect of conventional statistical significance ($p = 0.05$)
- **PKs from infants and toddlers, preschool-age children, school-age children, and adolescents:** Traditional or sparse sampling can be chosen, and for the parent drug and each metabolite, estimate bioavailability (area under the concentration-time curve), half-life, maximum concentration of drug in plasma (C_{max}), and time to C_{max} in the various age groups
- **Labeling change:** Appropriate sections of the label may be changed to incorporate the findings of the studies

CHANGES ADDED OR ELEMENTS MODIFIED IN SOME OR ALL NEW REQUESTS OR AMENDMENTS FROM 2001 TO 2003

- **Safety data:** One-year follow-up is specified, with all available information (published and unpublished) to include information on adverse events, growth (change in

head circumference, weight, length, or height), and development (milestones, school performance, neurocognitive testing) at baseline and 1 year.

- **Age groups:** 25 percent of participants should be infants to preschool age.
- **Race:** Black enrollment is specified to be 40 to 60 percent of total enrollment.
- **Age-appropriate formulation:** An age-appropriate formulation or documentation of an attempt to obtain an age-appropriate formulation, if the attempt was unsuccessful, is required.
- **Statistical considerations:** The ability to detect a 3-mm-Hg blood pressure change with 90 percent power is required.
- **Efficacy endpoints:** For the trial designs other than randomized withdrawal from active drug (see above), the primary efficacy measurement should be the change in blood pressure from baseline to the end of the treatment period plus the interdosing interval (trough). For randomized withdrawal trial designs, the primary efficacy measurement should be the change in blood pressure from the last on-treatment visit to the end of the withdrawal period.

CHANGES ADDED OR ELEMENTS MODIFIED, 2006

- **Interim analyses allowed to assess variability according to a prespecified rule to adjust the sample size to achieve the specified target power:** This interim analysis must be performed with >90 percent of the initially planned enrollment. Options for estimating variability are (1) a blinded, pooled analysis of all groups, (2) a blinded analysis of one group, or (3) a partially unblinded analysis within each group (performed by an independent third party).
- **Dissemination of information:** Summaries of medical and clinical pharmacology reviews are posted on the FDA website.

CHANGES ADDED OR ELEMENTS MODIFIED, 2009

- **Trial design:** Two types

    - *Type A:* randomized, double-blind parallel, placebo and two doses
    - *Type B:* two active doses with randomized withdrawal (same as Trial Design C described above but with two doses)

- **Statistical considerations:** The primary endpoint must be either absolute or the percent change in systolic or diastolic pressure. The statistical approach used will depend on the specific trial design; but broadly, the sponsor can allocate alpha to each active arm in the placebo-controlled comparison or to some combination of treatment arms (highest, two doses), or the sponsor can look for a positive slope in the dose-response relationship.
- **Sample size:** The trial program must have a total of no less than 200 patients in the 6- to 16-year-old age groups and no less than 50 patients in the l- to 5-year-old age groups.
- **Formulation:** If reasonable attempts to develop a commercially marketable formulation have failed, the sponsor must develop and test an age-appropriate

formulation that can be compounded by a licensed pharmacist, in a licensed pharmacy, from commercially available ingredients. The sponsor must document attempts and reasons that attempts failed. If the reasons are accepted and studies are conducted with the compounded formulation product, the label must include detailed compounding information.

- **Dissemination of information:** The written request and medical, statistical, and clinical pharmacology reviews will be posted on the FDA website, and the trial will be registered at ClinicalTrials.gov.
- **Labeling:** Regardless of whether the studies demonstrate that the drug is safe and effective or whether the results of such studies with the pediatric population are inconclusive, the sponsor must submit labeling to include information about the results of the studies.

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F
Committee and Staff Biographies

Thomas F. Boat, M.D. (*Chair*), is Vice President for Health Affairs and Christian R. Holmes Professor and Dean of the College of Medicine at the University of Cincinnati. He has been director of the Children's Hospital Research Foundation and chair of the College's Department of Pediatrics. He was also physician in chief of Children's Hospital Medical Center of Cincinnati. Dr. Boat is a member of the Institute of Medicine (IOM) and has served as member or chair of a number of IOM and National Research Council committees, most recently serving as chair of the Committee on Accelerating Rare Diseases Research and Orphan Product Development. A pediatric pulmonologist by training, Dr. Boat worked early in his career to define the pathophysiology of airway dysfunction and develop more effective therapies for chronic lung diseases of childhood, such as cystic fibrosis. More recently, he has worked at local and national levels to improve research efforts, subspecialty training, and clinical care in pediatrics. He is immediate past board president of the Association of Accreditation of Human Research Protection Programs, Inc. He has also served as chair of the American Board of Pediatrics, president of the Society for Pediatric Research, and president of the American Pediatric Society.

Peter C. Adamson, M.D., is professor of pediatrics and pharmacology at the University of Pennsylvania School of Medicine, chief of the Division of Clinical Pharmacology and Therapeutics at The Children's Hospital of Philadelphia (CHOP), and Director of Clinical and Translational Research at The Children's Hospital of Philadelphia Research Institute. He is board certified in pediatric hematology/oncology and in clinical pharmacology. Dr. Adamson's primary research focus is on pediatric cancer drug development. He served until 2008 as chair of the Children's Oncology Group (COG) Developmental Therapeutics Programs and principal investigator of the COG Phase 1 Consortium. He became chair-elect of COG on January 1, 2010. Prior to becoming the Director of Clinical and Translational Research at CHOP, he was the program director of the General Clinical Research Center and principal investigator of its Pediatric Pharmacology Research Unit, funded by the National Institute of Child Health and Human Development. He is codirector of the University of Pennsylvania-CHOP Clinical Translational Science Award. He was a member of the Institute of Medicine (IOM) committee on shortening the timeline for new cancer treatments and coedited the 2005 IOM report *Making Better Cancer Drugs for Children*. Most recently he served as a

member of the IOM Committee on Accelerating Rare Diseases Research and Orphan Product Development.

Richard E. Behrman, M.D., is a consultant to nonprofit health care and educational institutions. From 2002 to 2007, he was executive director of the Federation of Pediatric Organizations. Until July 1, 2002, he was Senior Vice President for Medical Affairs at the Lucile Packard Foundation for Children's Health and Senior Advisor for Health Affairs at the David and Lucile Packard Foundation. He continues clinical faculty appointments at the University of California, San Francisco, and George Washington University. He is a member of the Institute of Medicine (IOM) and has served as chair of the IOM Committee on Palliative and End-of-Life Care for Children, the Committee on the Ethical Conduct of Clinical Research Involving Children, and the Committee on Understanding Premature Birth and Assuring Healthy Outcomes. Dr. Behrman's areas of special interest include perinatal medicine, intensive and emergency care of children, the provision and organization of children's health and social services, and related issues of public policy and ethics. Among other publications, he has been editor in chief of the *Nelson Textbook of Pediatrics* (Elsevier).

F. Sessions Cole III, M.D., is Park J. White, M.D., Professor of Pediatrics and professor of cell biology and physiology, Washington University School of Medicine, and Chief Medical Officer, St. Louis Children's Hospital. He is a member of the Society of Pediatric Research, the American Society for Clinical Investigation, and the American Pediatric Society. Dr. Cole served on the Institute of Medicine Committee on Premature Birth, the Committee on the Ethical Conduct of Research Involving Children, and the Committee on Palliative Care for Children and Their Families, and he chaired the National Institute of Child Health and Human Development consensus conference panel on the use of inhaled nitric oxide therapy in premature infants. His areas of clinical interest include inherited lung diseases of infancy, surfactant protein B deficiency, newborn immunity, newborn infections, and family-centered care. Dr. Cole's research interests focus on the contributions of genetic variation in genes of the pulmonary surfactant metabolic pathway to the risk of neonatal respiratory distress syndrome.

Brian Feldman, M.D., M.Sc., is professor of pediatrics, medicine, and health policy, management and evaluation and professor of the Dalla Lana School of Public Health at the University of Toronto, where he has taught both critical appraisal (Introduction to Clinical Epidemiology) and advanced clinical trials courses for the past 14 years. He is also senior scientist and head, Division of Rheumatology, Hospital for Sick Children. Previously, Dr. Feldman was an Ontario Ministry of Health career scientist and held the Canada Research Chair in Childhood Arthritis. His areas of interest include the development of methods and measurement tools for the study of rare diseases and practical clinical trials in pediatric joint disease. Dr. Feldman currently holds research grants from Baxter Heathcare Corporation for the study of the burden of illness of severe hemophilia in Brazil and from Bayer Schering Pharma for the study of the outcomes of hemophilia prophylaxis. The grants are awarded through the Hospital for Sick Children under policies that provide for institutional ownership of the research data, information, and reports resulting from the research and for independence in the publication of

research findings. Dr. Feldman serves on a data monitoring committee for Novartis that, among other studies, monitors one pediatric study of canakinumab. He has been active in national and international rheumatic disease organizations, including the Canadian Arthritis Network, the Childhood Arthritis and Rheumatology Research Alliance, the International Hemophilia Prophylaxis Study Group, the Pediatric Rheumatology Collaborative Study Group, the Pediatric Rheumatology International Trials Organization, and the International Myositis Assessment Collaborative Study Group.

Pat Furlong, B.S.N., is the founding president and chief executive officer of Parent Project Muscular Dystrophy, the largest nonprofit organization in the United States solely focused on Duchenne muscular dystrophy (Duchenne). Its mission is to improve the treatment, quality of life, and long-term outlook for all individuals affected by Duchenne through research, advocacy, and education. Ms. Furlong is the mother of two sons who lost their battle with Duchenne in their teenage years. She has served on the boards of the Genetic Alliance and the Muscular Dystrophy Coordinating Committee (U.S. Department of Health and Human Services) and on the Data Safety Monitoring Board for both the Rare Diseases Clinical Research Network and the Cooperative International Neuromuscular Research Group. She was a member of the Institute of Medicine Committee on Accelerating Rare Diseases Research and Orphan Product Development. Currently, she serves on the Board of the National Organization for Rare Disorders and the Steering Committee of Treat NMD.

Eric Kodish, M.D., is the director of the Center for Ethics, Humanities, and Spiritual Care at Cleveland Clinic, where he holds the F.J. O'Neill Professor and Chair of Bioethics. He is executive director of the Cleveland Fellowship in Advanced Bioethics and professor of pediatrics at the Lerner College of Medicine of Case Western Reserve University. From 1993 to 2004, he cared for children with cancer and blood diseases at Rainbow Babies and Children's Hospital, where he was also the founding director of the Rainbow Center for Pediatric Ethics. Dr. Kodish has been principal investigator on a series of three National Institutes of Health (NIH)-funded multi-site studies of informed consent in childhood cancer. He served as chair of the Bioethics Committee of the Children's Oncology Group from 2002 to 2008, a member of the Committee on Bioethics of the American Academy of Pediatrics from 1999 to 2005, and director at large of the Association of Bioethics Program Directors from 2008 to 2010. He has also served on the NIH Recombinant DNA Advisory Committee and on the National Cancer Institute's Pediatric Central Institutional Review Board. He currently chairs the Board of Trustees of the Northeast Ohio Medical University (NEOMED). Among other publications, he is the editor of *Ethics and Research with Children: A Case-Based Approach* (Oxford University Press, 2005).

Jennifer Li, M.D., M.H.S., is professor of pediatrics (cardiology), professor of medicine (cardiology), and Director of Pediatric Clinical Research at the Duke Clinical Research Institute (DCRI); Core Director of Pediatrics at the Duke Translational Medicine Institute; and division chief of Pediatric Cardiology, Duke University Health System. In addition to her medical degree, she has a master's degree in clinical research. Under her leadership, the DCRI has coordinated multiple National Institutes of Health (NIH)- and

industry-sponsored projects in pediatric cardiology, rheumatology, infectious diseases, and neuropsychiatry. Dr. Li has also been the protocol chair and primary author of several industry-sponsored international multicenter studies, including studies to evaluate the safety and effectiveness of fosinopril doses in children with hypertension and to evaluate the pharmacodynamics and safety of clopidogrel in infants with cyanotic congenital heart disease and Blalock-Taussig shunts. Among other current activities, she is the principal investigator for the Duke/North Carolina Consortium of the National Heart, Lung, and Blood Institute-sponsored Pediatric Heart Network. She also serves on the Child Health Oversight Committee of the Clinical and Translational Sciences Award program at the National Institutes of Health and Pediatric Hypertension Treatment Working Group of the National Institute of Child Health and Human Development Best Pharmaceuticals for Children Act. She recently served as a special government employee to provide expertise in the analysis of safety in the pediatric population to the Office of Pediatric Therapeutics of the Food and Drug Administration (FDA) and contributed to analyses that supported legislation that expanded access to pediatric data submitted to the FDA.

Christina Markus, J.D., is a partner in the law firm of King and Spalding, where she is also deputy practice leader of the FDA and Life Sciences Group. Her practice focuses on the regulation of drugs, biologics, and other products by the Food and Drug Administration, the U.S. Drug Enforcement Administration, and related state agencies (e.g., boards of pharmacy). Ms. Markus represents companies and health care institutions in a range of regulatory compliance, enforcement, and business transactions involving product development and approval, marketing and advertising, and supply chain. She provides advice on operational, transactional, and enforcement issues in areas ranging from product research, development, and marketing approval to labeling and promotion, good manufacturing practice requirements, clinical trials registration, adverse event monitoring and reporting, licensure, distribution requirements, and market exclusivity and related protections.

Milap C. Nahata, Pharm.D., is division chair and professor, College of Pharmacy, and professor of pediatrics and internal medicine, College of Medicine, of the Ohio State University. He specializes in research on the effectiveness and safety of medications for a variety of human illnesses and is an expert in developing drug formulations for safe use by children. He has also studied drug stability and pharmacokinetics (the analysis of how pharmaceuticals are absorbed, distributed, metabolized, and eliminated by the body). Dr. Nahata is a member of the Institute of Medicine (IOM) and served on an IOM subcommittee that examined medications to treat children in emergency departments. He has received research achievement awards from both the American Association of Pharmaceutical Scientists and the American Pharmacists Association. Among many other publications, he is the author of three books on medications for pediatric patients.

Mark A. Riddle, M.D., is professor of psychiatry and pediatrics and director of the Children's Interventions Research Program in Psychiatry at the Johns Hopkins University School of Medicine. Dr. Riddle's research, teaching, and clinical practice focus on pediatric psychopharmacology, especially medication side effects. His publications

include more than 200 research articles, reviews, chapters, and edited volumes. He serves as a member of the National Institute of Child Health and Human Development-sponsored Data Monitoring Board for the Best Pharmaceuticals for Children Act and as a psychopharmacology consultant to the Task Force on Mental Health of the American Academy of Pediatrics. He is the principal investigator of a National Institute of Mental Health-sponsored, multisite study of interventions for children who have gained weight on antipsychotic medication and the site principal investigator of a 6-year follow-up study of preschoolers who were treated with medication for attention deficit-hyperactivity disorder. He was the director of the Division of Child and Adolescent Psychiatry at Johns Hopkins from 1993 to 2009 and was the founding chair of the National Institute of Mental Health's Review Committee on Interventions for Disorders Involving Children and Their Families.

Joseph W. St. Geme, III, M.D., is the James B. Duke Professor and Chair of Pediatrics and professor of molecular genetics and microbiology at Duke University Medical Center. Dr. St. Geme is an expert in the management of pediatric infectious diseases and in basic research on the molecular and cellular determinants of bacterial infection, with a focus on *Haemophilus influenzae* and *Kingella kingae*. He is a member of the American Society for Clinical Investigation, the Association of American Physicians, the American Academy of Microbiology, and the American Association for the Advancement of Science. He has served as president of the Pediatric Infectious Disease Society and was elected a member of the Institute of Medicine in 2010.

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