

LEGISLATION, REGULATIONS, AND GUIDANCES AFFECTING PEDIATRIC PHARMACOTHERAPY



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LEARNING OBJECTIVES

1. Distinguish between the major regulations and guidances affecting off-label drug use in pediatric patients.
2. Apply the concepts of extrapolation and interpolation to the issue of pediatric drug development.
3. Given the context related to the development of a new drug, distinguish whether a waiver of pediatric studies for a new drug is appropriate.
4. Distinguish between the pediatric drug development processes of the U.S. Food and Drug Administration (FDA) and that of the European Medicines Agency.
5. Apply guidances on pediatric drug development from the FDA or the International Conference on Harmonization when considering pediatric studies with a new drug or biological agent.
6. Assess the involvement of the National Institutes of Health in the Best Pharmaceuticals for Children Act.
7. Given a particular research study design, distinguish the appropriate category of risk and the special protections required for children by the National Research Act.

INTRODUCTION

Appropriate information on the dosing, efficacy, and safety of drugs used in pediatric patients has long been lacking. Some of the worst tragedies in drug therapy, such as those involving the elixir of sulfanilamide and thalidomide, have primarily affected children. These tragedies pointed out our lack of knowledge of appropriate

pediatric formulations and developmental toxicology; others, such as the Gray baby syndrome with chloramphenicol, demonstrated our lack of knowledge of developmental pharmacology.

One of the few benefits to come from our appalling lack of knowledge of how to use drugs in children has been legislation that improved the drug development system in the United States. However, these legislative acts have only recently been specifically directed to improving drug use in pediatric patients.

HISTORICAL BACKGROUND

Medical experiments in the 1700s often involved children. Edward Jenner, often called the “father of immunology,” tested the efficacy of his smallpox vaccine by first inoculating his own son and then 48 children in an almshouse in England. Around 1800, Benjamin Waterhouse, a Harvard professor, tested the smallpox vaccine on his own children by inoculating them and then exposing them to patients with smallpox. His experiment eventually included 19 vaccinated and 2 unvaccinated boys in Boston whom he intentionally exposed to smallpox. The vaccinated boys developed immunity; the unvaccinated boys died of smallpox. Other experiments involving children include those performed by Alfred Hess in his Hebrew Infant Asylum in New York, Louis Pasteur’s testing of diphtheria antitoxin in children from Paris orphanages, and Karl von Ruck’s tests of a tuberculosis vaccine (later found in guinea pigs to increase the risk

BASELINE REVIEW RESOURCES

The goal of PSAP is to provide only the most recent (past 3–5 years) information or topics. Chapters do not provide an overall review. Suggested resources for background information on this topic include:

- Kearns GL, Abdel-Rahman SM, Alander SW, Blowey DL, Leeder JS, Kauffman RE. Developmental pharmacology—drug disposition, action, and therapy in infants and children. *N Engl J Med* 2003;349:1157–67.
- Burckart GJ. Clinical pharmacology and biopharmaceutic considerations in pediatric global drug development. *Am Pharm Rev* 2009;12:31–4.

ABBREVIATIONS IN THIS CHAPTER

BPCA	Best Pharmaceuticals for Children Act
CFR	Code of Federal Regulations
FDAAA	FDA Amendment Act of 2007
FDAMA	FDA Modernization Act of 1997
ICH	International Conference on Harmonization
IRB	Institutional Review Board
NDA	New drug application
PPSR	Proposed Pediatric Study Request
PREA	Pediatric Research Equity Act

of contracting tuberculosis) in children at an orphanage in North Carolina. As recently as the 1950s and 1960s, research on hepatitis used mentally retarded children at Willowbrook State School in New York.

Eventually, the pendulum swung the other way, and children were excluded from drug development programs, thus preventing the specific study of drugs in pediatric patients. In 1968, Dr. Harry Shirkey created the term *therapeutic orphans* to describe this situation. The lack of drug studies in children created a system in which pediatricians had to make difficult decisions about the risks, and benefits of using a drug in a child when no information on dosing, efficacy, or safety in the pediatric population was available. That lack of information was reflected by the absence of pediatric dosing information in U.S. Food and Drug Administration (FDA)-approved labeling, which meant these drugs were being used off-label. At the time of Shirkey's declaration, about 80% of all drugs had no labeled indications for use in pediatric patients.

The research in children at Willowbrook, together with other excesses in adults such as the Public Health Service's syphilis trials, eventually led to the passage in 1974 of the National Research Act. This act established the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. The next 30 years saw the creation of pediatric clinical pharmacology as a discipline.

Prominent pediatric physicians and pharmacists worked to establish a pharmacokinetic basis for drug dosing in children, laying the groundwork for understanding the ontogeny of drug metabolism and the renal elimination of drugs in pediatric patients. A growing concern was that, although the National Research Act subpart D protected children as human research subjects, it might provide a reason to exclude children from research trials. By 1998, little progress had been made in developing sufficient information for the FDA to label drugs specifically for pediatric use. A 1999 report

concluded that more than 70% of all drugs listed in the *Physicians' Desk Reference* were not labeled for use in pediatric patients.

Around that time, a regulatory approach to correct the lack of pediatric drug studies and information available was devised. In 1994, the FDA had requested that sponsors provide all available drug information on the use of their drugs in pediatric patients. The intent of this action was to allow labeling of drugs for use in pediatric patients if sufficient scientific information was available. However, the program was unsuccessful in obtaining sufficient information for most drugs.

In 1997, the FDA Modernization Act (FDAMA) included an incentive for sponsors whose drugs were studied in pediatric patients. If the sponsors performed pediatric studies, they received an extra 6 months of patent exclusivity for their drug. Biologics were not eligible for the program, but all other investigational and approved drugs could receive the extra patent life. In 2002, these incentives were renewed under the Best Pharmaceuticals for Children Act (BPCA).

In 1998, the National Institutes of Health (NIH) published the NIH Policy and Guidelines on the Inclusion of Children as Participants in Research Involving Human Subjects. Also that year, the FDA promulgated the Pediatric Rule requiring all Biologic License Applications, new drug applications (NDAs), and supplemental applications to include pediatric safety and effectiveness data. The Pediatric Rule was enforced if the application had a new active ingredient, indication, dosage form, dosage regimen, or route of administration. The studies conducted under the Pediatric Rule were also eligible for the patent extension provided by the FDAMA. Therefore, the FDA's pediatric program provided both a requirement and a financial incentive to meet this requirement.

In 2000, the Association of American Physicians and Surgeons, the Competitive Enterprise Institute, and Consumer Alert sued the FDA, claiming the agency did not have the legislative authority to enforce the Pediatric Rule. In 2002, a federal court in Washington, D.C., struck down the Pediatric Rule. Then-Secretary of Health and Human Services Tommy G. Thompson immediately worked with Congress to codify the basic tenets of the Pediatric Rule. In 2003, Congress enacted the Pediatric Research Equity Act (PREA) to ensure that new drugs intended for use in children would be studied in children.

Historically, the FDA has put considerable emphasis on labeling for pediatric uses; this is not because of the regulatory process of labeling but because of the evidentiary standards required by the FDA to substantiate labeling. Under these legislative acts, pediatric studies are performed and drugs are labeled for use in pediatric patients; therefore, the off-label use of drugs in pediatric patients is one measure of success of these acts. Every

clinician realizes that most drugs are used off-label (i.e., for indications for the pediatric population not included in FDA-approved labeling). Although information on the efficacy and safety of many drugs has been developed through studies, many of these pediatric off-label uses still lack adequate information on pediatric dosing, efficacy, and safety.

IMPORTANT REGULATIONS RELATED TO PEDIATRIC DRUG THERAPY

National Research Act

The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research was formed by the passage of the National Research Act in 1974. One of the commission's charges was to identify the requirements for informed consent to participate in biomedical or behavioral research in children. The resulting 1977 report, *Research Involving Children*, was translated into regulations as 45 Code of Federal Regulations (CFR) 46 (subpart D) – Additional Protections for Children as Research Subjects.

According to the commission's report, research in children would be classified according to the risk and benefit to the child participating. As the risk-to-benefit ratio of the research became less favorable for the participating child, additional protections would be needed. These categories were written into sections 45 CFR 46.404–407 of subpart D of the regulations. Research involving minors must fit into one of four risk categories to be approved by an Institutional Review Board (IRB); Table 1-1 lists these risk categories, along with their definitions, examples, and special considerations. In addition, section 45 CFR 46.409 restricts the involvement of wards of the state in research that entails greater than minimal risk and that is without direct subject benefit.

For a child to participate in research, consent (permission) of one or both parents is required, depending on the risk assessment; also required, in most cases, is assent (agreement) of the child. According to 45 CFR 46.401, merely failing to object should not be construed as assent. Not all children are capable of giving assent; the local IRB is responsible for determining the age of assent and when assent is an absolute requirement. A waiver of consent or assent is possible in studies approvable under CFR 46.404 (minimal risk) but not for studies in the other categories.

Pediatric Research Equity Act

The PREA is the modern-day version of the Pediatric Rule. The PREA was extended for 5 years under the FDA Amendment Act of 2007 (FDAAA) and is now scheduled to expire on October 1, 2012. The PREA requires sponsors to submit a pediatric assessment with every application to the FDA. The pediatric assessment

discusses the potential use in pediatric patients, a current understanding of the risk/benefit ratio in pediatric patients, and whether studies should be waived or deferred in any age group. If the application meets one of the five criteria described above under the Pediatric Rule, the requirements of the PREA are activated and must be followed. If the pediatric assessment concludes that pediatric studies are to be deferred until after adult approval, then a pediatric plan is required for deferred pediatric studies. Otherwise, pediatric studies meeting the PREA requirements should be submitted before the approval of the adult application.

Under Title IV of the FDAAA, tracking of studies under the PREA and BPCA is required, together with data on labeling changes produced under these legislative acts. The complete medical, statistical, and clinical pharmacology reviews for pediatric submissions under the BPCA and PREA are available on the FDA Web site. An annual review of all studies under the PREA is now conducted and publicly available. An FDA Pediatric Review Committee was established that reviews all applications to ensure they fulfill the requirements of the PREA before approval. The FDA Pediatric Review Committee is a multidisciplinary group composed in part of pediatricians from the Pediatric and Maternal Health Staff, FDA Center for Drug Evaluation and Research; of pediatricians of the Office of Pediatric Therapeutics, FDA Commissioner's Office; and of pediatric clinical pharmacologists and pharmacometricians from the FDA Office of Clinical Pharmacology.

The pediatric plan to perform deferred studies after adult approval is a postmarketing requirement. This is in contrast to a postmarketing commitment, which is not considered a requirement. Before a drug's approval for use in adults, the pediatric plan should be complete and based on modeling and simulation of all available data for the drug.

Best Pharmaceuticals for Children Act

The BPCA, which was also extended for 5 years under the FDAAA, is scheduled to expire on October 1, 2012. The NIH plays a large role in the BPCA because when the FDA issues a written request for drug studies in children under the BPCA, and the written request is not accepted by the sponsor, the NIH considers funding the studies. Most of the drugs considered by the NIH are off-patent, so no patent exclusivity could be gained by conducting pediatric studies. The NIH annually conducts a BPCA meeting that brings together several pediatric constituencies and sets priorities for NIH funding of pediatric studies for the coming year. The NIH works closely with the FDA and submits Proposed Pediatric Study Requests (PPSRs) to the FDA for consideration.

A PPSR can also be submitted to the FDA by the sponsor developing a new drug. In this case, the sponsor has a financial incentive to perform the pediatric studies in

Table 1-1. Categories of Approvable Research in Children

Category	Definition	Examples	Special Considerations
No greater than minimal risk ^a (45 CFR 46.404)	The probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests	Retrospective or prospective collection of information obtained during the course of standard care. Examples of minimal risk procedures include venipuncture, non-sensitive material surveys, and chest radiographs	Consent of one parent and assent of the child are required Waiver of consent and/or assent can be obtained if approved by the IRB
Greater than minimal risk with possible direct benefit to the individual subject (45 CFR 46.405)	Possible benefit must balance or outweigh increased risk; the risk-to-benefit ratio for the individual must be at least as favorable as available alternatives	Use of two agents with similar efficacy but different costs; evaluation of two similarly effective agents, one that might be effective in fewer days of treatment	Consent of one parent and assent of the child are required. If the research could have direct benefit to the child that is unavailable outside the research, the consent of the parent is sufficient
Greater than minimal risk with no direct benefit but likely to produce generalizable knowledge about the subject's disorder/condition (45 CFR 46.406)	The risk must represent only a minor increase over minimal risk. The intervention or procedure presents experiences that are reasonably commensurate with those inherent in their actual or expected medical, dental, psychological, social, or educational situations. Knowledge gained should be of vital importance for understanding or amelioration of the subject's disorder/condition	Additional provoked sputum cultures in children with cystic fibrosis; additional radiologic scans in children with solid tumors; urine sample obtained by catheterization in children with neurogenic bladder; additional cerebrospinal fluid samples from children with ventriculoperitoneal shunts	Permission of both parents and the assent of the child are required
Research otherwise not approvable (45 CFR 46.407)	Must provide a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children. For federal funding: requires review by a panel of experts appointed by the U.S. Secretary of Health and Human Services		Permission of both parents and assent of the child are required

^aMinimal risk is weighed against the standard of the life of a healthy child, not of the child involved in the research.

CFR = Code of Federal Regulations; IRB = Institutional Review Board.

Information from: Code of Federal Regulations. Title 45: Public Welfare. Department of Health and Human Services. Part 46: Protection of Human Subjects. Revised January 15, 2009. Available at www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm.

the form of an additional 6 months of patent exclusivity if the terms of the written request are fulfilled. The written request is viewed as a contract in this situation, and an Exclusivity Board at the FDA evaluates whether the sponsor has fulfilled the terms of the written request sufficiently to get the additional patent exclusivity.

The FDAAA increased the BPCA's authority in two ways. Under BPCA, the FDA can now issue a written request that covers more than one indication for a drug and can capture both on- and off-label uses of the medication in pediatric patients. Under the BPCA, pediatric studies must be submitted and exclusivity awarded at least 9 months before the patent expires. The FDA has 6 months to review submitted BPCA studies; therefore a BPCA study must be submitted at least 15 months before patent expiration to be eligible for the added 6 months of patent exclusivity. All associated FDA-issued written requests are made public after a drug has been granted exclusivity.

Through November 2008, the FDA had issued 360 written requests for pediatric studies under BPCA. Labeling changes were made on the basis of pediatric information provided in response to 159 written requests. In 95 written request responses, the labeled age for use was expanded, and in 45 responses, new or expanded pediatric safety information was added to the label. Only 27 labels reported a specific dosing change or adjustment. Pediatric safety and efficacy were not established in 50 of the changed labels because even failed pediatric studies (defined as a pediatric study that does not demonstrate drug efficacy) must be reported in labeling under the FDAAA.

The Orphan Drug Act

The Orphan Drug Act was enacted to support the development of products for rare diseases, defined as those occurring in fewer than 200,000 people in the United States and for which there is little hope of recovering drug development costs. Many rare diseases occur in children, either because of inborn errors of metabolism or because of cancers that occur only in pediatric patients.

The FDA's Office of Orphan Products Development oversees the Orphan Drug Research Grants program. These grants are designed to support clinical trials and include studies of drugs, biologics, medical foods, and medical devices. This area of drug development is increasingly active, and 160 products have been designated for orphan diseases and conditions. The FDA approved 17 orphan drug products in 2009, most of which were for pediatric use or combined pediatric and adult use.

The PREA does not apply to Orphan Drug Products; however, a written request under the BPCA can be issued for an Orphan Drug Product. No requirement for pediatric studies of Orphan Drug Products exists, so either the

sponsor has to respond to a written request or the NIH has to fund pediatric studies of these products.

EUROPEAN MEDICINES AGENCY

In 2000, the European Parliament adopted a resolution calling for better medicines for children, opening the way for new regulation. In December 2006, the European Parliament created the European Medicines Agency's Pediatric Committee and provided the same 6-month patent extension as in the BPCA. In January 2007, the European Union's new pediatric regulation went into effect.

The European Medicines Agency requires a sponsor to submit a Pediatric Investigational Plan at the end of phase I of drug development. This plan allows the agency to view a pediatric assessment much earlier than the FDA, which may not see the assessment until an NDA or Biologic License Application is submitted for marketing approval. The Pediatric Investigational Plan can then be modified on the basis of any emerging findings during the later stages of drug development through discussions with the European Medicines Agency's Pediatric Committee.

The FDA's Office of Pediatric Therapeutics and the European Medicines Agency's Pediatric Committee work together closely on issues that arise during pediatric reviews. However, each pediatric committee makes independent decisions; thus, sponsors must communicate with each agency before initiating pediatric studies.

GUIDANCES RELATED TO PEDIATRIC DRUG DEVELOPMENT

Drug development programs for children may be initiated as a response to the requirement under PREA to conduct pediatric studies for a drug developed in adults; they may also be initiated to develop a drug product for a specific pediatric indication. Several guidances are available for those involved in pediatric drug development programs. These guidances are important both to clinicians designing and participating in pediatric drug development trials and to the pharmaceutical industry supporting these trials. Some of the most important guidances are reviewed as follows.

International Conference on Harmonization E11: Clinical Investigation of Medicinal Products in the Pediatric Population

Although published in 2000, this guidance remains important to international pediatric drug development. The guidance lays out criteria for considering a pediatric drug development program, such as the prevalence of the condition to be treated, seriousness of the condition, availability of alternative treatments, development

of specific pediatric end points, and developmental safety concerns. Specific pediatric end points are primary efficacy criteria that are not applicable in adult patients and that could be either a biomarker or a direct clinical outcome.

Considerations for pediatric pharmacokinetic studies are listed in the International Conference on Harmonization (ICH) E11, as are the age classifications for pediatric patients. Care should be used in preparing documents for the FDA because ICH E11 is not an FDA document and is not intended to address the regulatory requirements in a specific country. For example, some details in ICH E11 such as the age classification of adolescents may vary between the FDA and the European Medicines Agency.

**FDA Guidance for Industry
Exposure-Response Relationships – Study Design,
Data Analysis, and Regulatory Applications**

This guidance is important because it is often used in developing and analyzing pediatric studies. Population

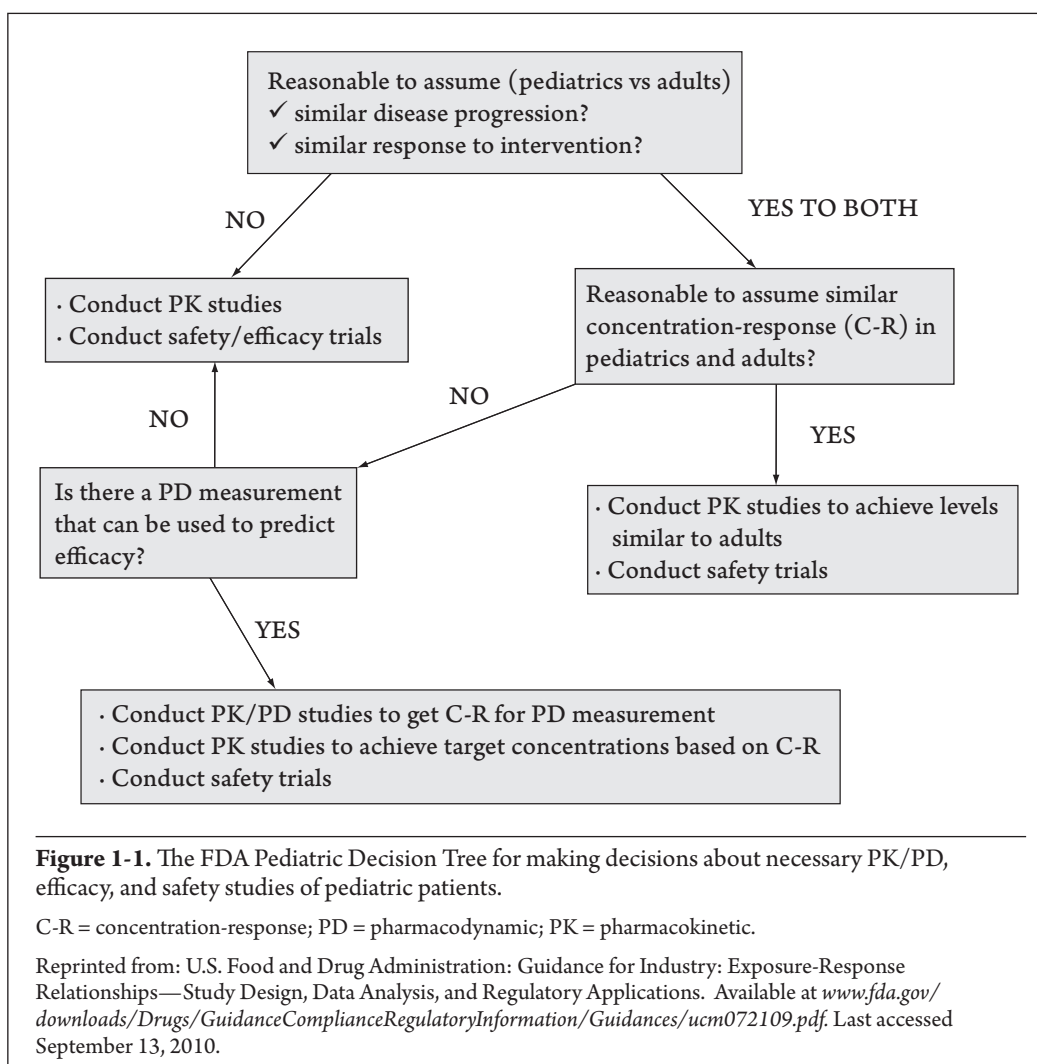
pharmacokinetics, modeling, and other considerations important to pediatric studies are covered in this guidance.

Appendix B of this guidance contains the FDA’s Pediatric Study Decision Tree (Figure 1-1). The Decision Tree provides a guide to deciding whether only a pharmacokinetic study is required in pediatric drug development, whether a pharmacokinetic-pharmacodynamic study is required, or whether a pharmacokinetic and efficacy study is required.

How to Comply with the PREA

This guidance is a systematic guide to compliance with the PREA; it discusses the pediatric assessment, when to develop a pediatric plan, what ages to cover in a pediatric plan, and product formulation issues. For example, if an age-appropriate formulation is unavailable from the sponsor, the sponsor must demonstrate legitimate attempts to create a pediatric formulation of the drug product.

The guidance discusses why a waiver of pediatric studies is granted, including the following. (1) The necessary



studies are impossible or highly impractical (e.g., the number of patients is small or the patients are geographically dispersed). (2) Evidence strongly suggests that the drug/biological product would be ineffective or unsafe in all pediatric age groups. (3) The drug or biological product either does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients or is unlikely to be used in a substantial number of pediatric patients. If a waiver is granted on the basis of evidence that the drug is unsafe or ineffective in pediatric populations, the applicant must include this information in the labeling for the drug or biological product.

The required steps in FDA approval, as they pertain to pediatric drug development, are illustrated in Figure 1-2.

IMPORTANT CONCEPTS

Several concepts are critical to understanding how legislative acts can be used to obtain the information needed to determine an appropriate pediatric dose and to obtain critical data for the safe and effective use of a new drug in children.

Extrapolation and Interpolation

Extrapolation is the application of efficacy data from adult studies to pediatric patients. Although this may seem like a simple concept, the extrapolation of data is complex. One of the first considerations is whether the disease process is the same in adults and children. An example of extrapolation that is generally considered appropriate is when an infectious disease occurs in both children and adults. However, some diseases such as asthma may appear to be similar but have underlying pathophysiology that is different in children than in adults. The responsiveness of a particular disease to drug therapy is another measure by which clinicians can evaluate the appropriateness of extrapolation.

Extrapolation is important to avoid unnecessary studies of pediatric patients. The discussion of extrapolation in U.S. legislation is explicit so that studies of pediatric patients will be conducted only if they are necessary and have a specific purpose in building the scientific basis for drug approval in pediatric patients.

Interpolation is the process of estimating pediatric drug doses in an age group after the dosages of younger and/or older pediatric patients have been established by thorough clinical pharmacology studies.

Pharmacokinetics and Pharmacodynamics

If the efficacy of a drug to treat a specific disease process can be extrapolated, then matching pediatric drug exposure to adult exposure to the drug is the approach most often taken to determine an appropriate pediatric dose. Pharmacokinetic/pharmacodynamic studies may be the only chance to arrive at a safe and effective dose in pediatric patients.

Numerous pediatric studies conducted under BPCA have failed to achieve pediatric labeling. Therefore, considerable planning and the use of all available data in adults are required. Modeling and simulation are essential tools that can increase the likelihood of a successful trial. Members of the FDA's Office of Clinical Pharmacology have described the use of these techniques in pediatric drug development.

Pediatric Drug Safety

It is impossible to extrapolate the pediatric safety information needed for labeling from adult data. Nevertheless, the number of patients involved in pediatric safety studies is typically only a fraction of the number involved in adult drug safety studies. Therefore, the opportunity to detect infrequent adverse events in pediatric drug trials is compromised. Even when pediatric safety information is included in the drug labeling, the public reporting of drug safety studies is inadequate. The electronic collection of pediatric patient data from clinics and hospitals may provide a source for better postmarketing surveillance for adverse events in the future.

THE FUTURE OF PEDIATRIC DRUG DEVELOPMENT

Regulatory and legislative movements to improve drug therapy for pediatric patients began about 15 years ago. These movements have resulted in an increase in the number of pediatric studies performed and in the inclusion of specific labeling for pediatric patients in FDA-approved labels. Even so, a 2009 study of pediatric outpatients found that 62% still received drugs for off-label uses, with 96% of cardiovascular medications still off-label for use in pediatric patients. In addition, there continue to be few studies performed in children younger than 1 year.

Developing the evidence related to a drug's dosing, efficacy, and safety in pediatric patients continues to be a challenge. A primary difficulty is the small number of pediatric patients who can be recruited for any protocol. Renewed interest in developing small clinical trials that still meet the evidentiary standards of the FDA has been stimulated by the FDA's Office of Orphan Products Development and the NIH's Office of Rare Diseases Research. These two governmental offices have sponsored a yearly course on the development of small clinical trials using advanced trial design concepts, such as an enriched design or adaptive trials.

The regulatory processes that come under the PREA and BPCA provide the carrot and stick for pediatric drug development studies, but making the system work well requires the efforts of clinical investigators and scientists who desire to improve pediatric studies. The pharmacometric tools to provide modeling and simulation already

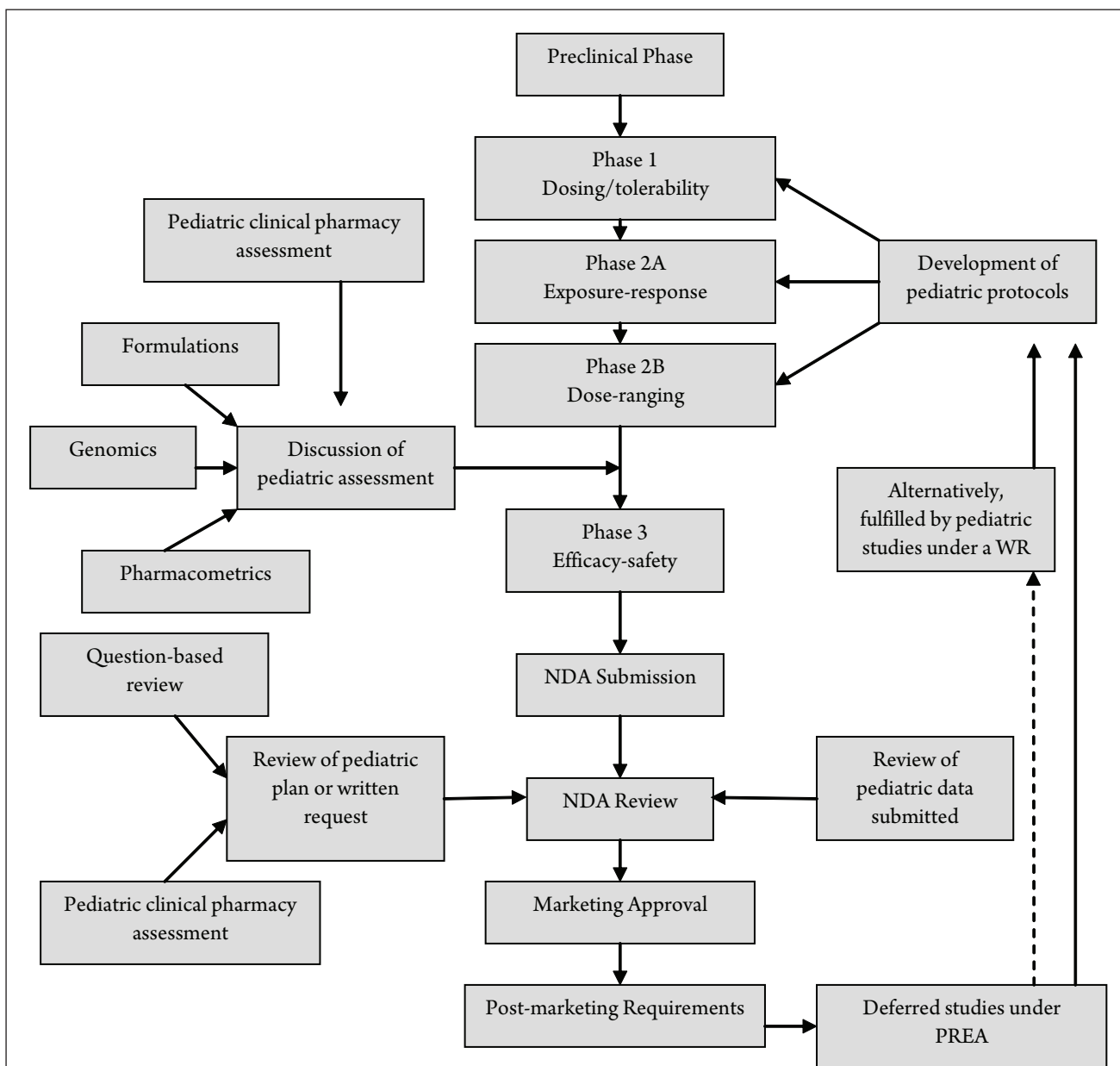


Figure 1-2. The flow of the discussion and evaluation of pediatric studies in drug development. Discussion between the sponsor and the FDA should ideally occur at the end of phase 2, with input from multiple disciplines. Evaluation of the Pediatric Plan or Written Request occurs after NDA submission. If pediatric studies are deferred under PREA, this requirement can be met by pediatric studies that are conducted under a written request.

FDA = U.S. Food and Drug Administration; NDA = new drug application; PREA = Pediatric Research Equity Act; WR = Written Request.

exist but must be applied early in the drug development process.

With the success of these initiatives, the next 10 years will produce more studies that identify effective therapies and optimal dosages for pediatric patients. Significant efforts to improve the quantity and quality of drug safety data are also expected. It is also to be hoped that the therapeutic orphan status will finally be relegated to pediatric drug development's history rather than remaining its challenge.

ANNOTATED BIBLIOGRAPHY

1. Abdel-Rahman SM, Reed MD, Wells TG, Kearns GL. Considerations in the rational design and conduct of phase I/II pediatric clinical trials: avoiding the problems and pitfalls. *Clin Pharmacol Ther* 2007;81:483–94.

This study discusses the appropriate design of pediatric studies during drug development. Although more studies in children are now conducted under the PREA and BPCA, only two or three pediatric studies per drug application are typically submitted to the FDA to support labeling related to pediatric dosing, efficacy, and/or safety. Therefore, it is imperative that the design of such studies be optimal to obtain the best information possible. The main sections of the article include selecting the pediatric patient population, selecting the dosing approach, choosing the means of drug administration, measuring drug concentrations, monitoring tolerability and safety, analyzing the data, and considering protocol elements. The authors pose critical questions under each section and provide examples of good and bad practices. Individuals who will be involved in early phase drug development in pediatric patients will find this article invaluable.

2. Bazzano AT, Mangione-Smith R, Schonlau M, Suttrop MJ, Brook RH. Off-label prescribing to children in the United States outpatient setting. *Acad Pediatr* 2009;9:81–8.

Harry Shirkey coined the term *therapeutic orphans* in 1968, when about 80% of all drugs were not FDA-labeled for use in children. With the approval of the PREA and BPCA, this number should be reduced dramatically. However, there remains much resistance to conducting the appropriate pediatric studies to obtain labeling. Therefore, the monitoring of off-label use of drugs in children is an important measure of progress. A drug is only FDA-labeled for use in a specific group of pediatric patients if the studies related to drug dosing in one or more pediatric age groups have shown efficacy or if efficacy has been extrapolated, optimal dosing has been established through appropriate pharmacokinetic or pharmacodynamic studies, and pediatric safety studies have been conducted. If this FDA-approved labeling for a specific indication in pediatric patients has not been established, the use of that drug in a pediatric patient for that indication is considered off-label.

This article is one of the most recently published studies on off-label drug use, although it uses data collected from 2001 to 2004. The study addresses outpatient drug

use, which represents the largest area of pediatric drug use. In the estimated 312 million pediatric outpatient visits, 62% (193.5 million visits) involved the child getting a prescription for at least one drug for an off-label use. The most problematic areas were cardiovascular agents, in which more than 90% of visits had an off-label drug prescribed; and gastrointestinal and pain relief agents, in which more than 80% of visits had an off-label drug prescribed. Of importance, off-label use of drugs in children should continue to be monitored as a measure of success in conducting appropriate pediatric studies during drug development.

3. Benjamin DK Jr, Smith PB, Jadhav P, Gobburu JV, Murphy MD, Hasselblad V, et al. Pediatric antihypertensive trial failures: analysis of end points and dose range. *Hypertension* 2008;51:834–40.

This study examines six pediatric trials involving anti-hypertensive agents that were performed between 1998 and 2005. The study provides a good analysis of what works to obtain efficacy and safety data in children so that a drug can be FDA-labeled for pediatric use. The six trials included studies evaluating amlodipine, enalapril, fosinopril, irbesartan, lisinopril, and losartan. Proof of efficacy was achieved for only three of the six drugs (i.e., enalapril, lisinopril, and losartan). In comparing the successful and unsuccessful trials, there were differences in the primary end point, dosing range, and availability of a pediatric formulation. The trials that succeeded used diastolic blood pressure as the end point, used a wide range of nonoverlapping doses to establish appropriate dosing, and had a pediatric dosage form available to allow appropriate adjustments for varying body weights in children.

4. Benjamin DK Jr, Smith PB, Sun MJ, Murphy MD, Avant D, Mathis L, et al. Safety and transparency of pediatric drug trials. *Arch Pediatr Adolesc Med* 2009;163:1080–6.

Very few studies have specifically examined pediatric drug safety. This study evaluated drugs studied from 1997 to 2007 for which information was submitted to the FDA for pediatric exclusivity patent extension. Of 137 FDA-approved labeling changes, 33 were for safety reasons. Of the 33 trials, 17 were not published in the peer-reviewed literature and have only the information in the FDA-approved labeling publically available. Sixteen studies dealing with pediatric drug safety were published in the peer-reviewed literature, but seven had information in the published report that was substantially different from that reported to the FDA. Additional transparency is needed for pediatric safety studies conducted under the PREA and BPCA so that public scrutiny of these studies is possible.

5. Jadhav PR, Zhang J, Gobburu JV. Leveraging prior quantitative knowledge in guiding pediatric drug development: a case study. *Pharm Stat* 2009;8:216–24.

This article builds on the article discussed in bibliography 4 by providing insight into the use of clinical trial simulations to design effective pediatric trials. The data used for the case study come from one of the

antihypertensive trials reviewed by Benjamin. An exposure-response model, a placebo-response model, and a dropout model were used. Mixed-model, repeated-measures design with the assumption of multivariate normal distribution was used for primary analysis. Using previous study data in adults, the clinical trial simulation allowed an exploration of the ranges of drug sensitivity, as well as the number of pediatric patients required in such a trial. The authors conclude that clinical trial simulation should be an essential and routine part of designing trials for pediatric patients.

6. Goodkin HP, Buck ML. Still orphans: antiepileptic drug trials in children under 2 years of age. *Neurology* 2008;70:2093–4.

This editorial makes two important points. The first issue is that although the PREA and BPCA have facilitated many more studies of children, very few of these trials have involved children younger than 2 years. The other point made involves the discussion of a study in the same issue of the journal that examined lamotrigine use in children younger than 2 years with a seizure disorder. The lamotrigine study used an enriched responder design so that a smaller patient population would be necessary, resulting in fewer patients being exposed to the use of a placebo. Although the trial did not show a significant effect of lamotrigine on the primary end point, the authors viewed the outcome as supporting the idea that newer trial designs can be effective for studies of younger children.

7. Johnson TN, Rostami-Hodjegan A, Tucker GT. Prediction of the clearance of eleven drugs and associated variability in neonates, infants and children. *Clin Pharmacokinet* 2006;45:931–56.

One tool available for predicting drug clearance in pediatric patients and for designing pediatric trials is physiologically based pharmacokinetic modeling. A commercial software package is available for this type of modeling. In this study, the authors predicted the clearance for 11 drugs for children ranging from newborns to 18 years of age. Several drugs, including those that are highly metabolized and renally eliminated, were included. The model included estimates of body surface area, cardiac output, liver volume, liver blood-flow, ontogeny of the cytochrome P450 enzymes, kidney function, plasma protein binding, first-pass gut metabolism, and pharmacogenetics. In neonates, 70% of predicted clearance values were within 2 times the observed values. Some assumptions made in this type of modeling are discussed. Overall, physiologically based pharmacokinetic modeling is useful for designing drug trials for pediatric patients, but all estimates derived by modeling must be confirmed by well-designed clinical trials.

8. Li JS, Eisenstein EL, Grabowski HG, Reid ED, Mangum B, Schulman KA, et al. Economic return of clinical trials performed under the pediatric exclusivity program. *JAMA* 2007;297:480–8.

This study examined nine drugs studied from 2002 to 2004 that received a 6-month patent extension under the BPCA program. The objective was to examine the benefit-to-cost ratio for each drug. The cost of performing the drug studies of children was weighed against the potential return on the exclusivity obtained by performing them. Only one blockbuster drug used for gastroesophageal reflux had a very high benefit-to-cost ratio. The other drugs had small to modest benefit-to-cost ratios. The authors' conclusion was that reducing the 6-month patent extension further would have deleterious effects on the sponsor's willingness to conduct pediatric clinical trials. Performing pediatric studies earlier during the drug development process will help ensure economic benefits to sponsors so that sufficient patent time is available to submit the necessary pediatric data to the FDA.

9. Rodriguez W, Selen A, Avant D, Chaurasia C, Crescenzi T, Gieser G, et al. Improving pediatric dosing through pediatric initiatives: what we have learned. *Pediatrics* 2008;121:530–9.

This article reviews pediatric labeling changes and submissions under the BPCA from 1998 to 2005. Because of these studies, 108 drugs had FDA-approved labeling changes reflecting pediatric information. Around 23 drugs had the addition of pharmacokinetic information, 34 had new safety information, 19 had information regarding the lack of efficacy in pediatric patients, 12 had information on a pediatric formulation, and 77 extended the age range for pediatric use. The authors provide 16 examples that include agents with decreased clearance in younger patients, agents with increasing clearance with increasing body weight, and drugs with higher apparent oral clearance in younger patients. These trials continue to add to a valuable database of information on the proper design of successful clinical trials in pediatric patients.

10. Vassal G. Will children with cancer benefit from the new European Paediatric Medicines Regulation? *Eur J Cancer* 2009;45:1535–46.

This article reviews the European Union's process related to pediatric drug development in the area of oncology. The discussion shows the universality of the problem of pediatric drug development, especially in the treatment of cancer in children. As mentioned previously, 75% of the drugs used in children with cancer are used off-label. In addition, the list of disease processes for which automatic waivers for pediatric studies will be granted mainly centers on adult tumors that do not occur in children. Unlike many other pediatric diseases that have an adult counterpart, pediatric tumors are often histologically distinct from adult tumors. Therefore, it would be easy for drug developers to avoid the entire issue of drug therapy for cancer in children. The author suggests that a pediatric waiver not be granted based on histology but rather on the mechanism of drug action. An example given is breast cancer, in which the target of drug therapy may in fact be present in some tumors encountered in children.

11. Department of Health and Human Services, Code of Federal Regulations. Title 45 Public Welfare; Part 46: Protection of Human Subjects. Revised January 15, 2009; effective July 14, 2009. Available at www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm. Accessed August 23, 2010.

This document, available on the U.S. Department of Health and Human Services (HHS) Web site, provides subparts A–E of the 45 CFR 46: Protection of Human Subjects. As mentioned previously, subpart D addresses the additional protections that must be in place for the protection of children involved as subjects in research. The term *children* in this document refers to individuals who have not attained the legal age of consent to treatments or procedures involved in the research, under the applicable law of the jurisdiction in which the research will be conducted. Subpart A provides HHS's basic policies for protection of human subjects including defining research, exempt research, and other forms of research. The requirement for an IRB to review research for compliance with these policies is established in this section. All policies related to the membership and activities of IRBs are given here. Subpart B deals with additional protections for pregnant women, human fetuses, and neonates. Subpart C addresses the unique protections required for biomedical and behavioral research involving prisoners. Finally, subpart E addresses IRB registration.