Most medicines have never been adequately tested for safety and efficacy in pediatric populations and preterm, infants and children are particularly vulnerable to adverse drug reactions.


This new edition covers the legal and ethical issues of consent and assent, the additional legal and safety protections for children, and the appropriate methods of surveillance and assessment for children of varying ages and maturity, particularly for patient reported outcomes. It includes new developments in biomarkers and surrogate endpoints, developmental pharmacology and other novel aspects of global pediatric drug development. It also encompasses the new regulatory initiatives across EU, US and ROW designed to encourage improved access to safe and effective medicines for children globally.

From an international team of expert contributors Pediatric Drug Development: Concepts and Applications is the practical guide to all aspects of the research and development of safe and effective medicines for children.
Pediatric Drug Development
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Preface

“A hundred children, a hundred individuals who are people – not people-to-be, not people of tomorrow, but people now, right now – today.”

Janusz Korczak, How To Love A Child

I learned a number of years ago about Janusz Korczak (1878–1942), a children’s advocate, who spoke of a Declaration of Children’s Rights long before any such document was drawn up by the Geneva Convention (Korczak, 1924) or the United Nations General Assembly (Korczak, 1959), through my mentor and friend, Steven Spielberg, MD, PhD. The spirit expressed in these words underlies the passion for the revitalization and refreshment of this second edition of Pediatric Drug Development.

The decision to edit a second version is, for any book, one that takes months of preparation and engagement with the publisher. Wiley has been enthusiastic in supporting us and we mutually believe that the need to discuss new issues in pediatric drug development was critical. Much has happened in the regulatory environment to continue to encourage and promulgate specific protection of infants and children. Particularly, the newly permanent Food and Drug Administration Safety and Innovation Act (FDASIA) has made permanent legislation to facilitate drug development for children, known as the Best Pharmaceuticals for Children Act (BPCA) and requirements for pediatric studies under the Pediatric Research Equity Act (PREA) from 2003.

This second edition reviews the impact of this new legislation but also reenergizes the reader to understand the scientific principles and practice required to synthesize the most effective drug development programs for children. New topics are covered that reflect developments in regulatory and technological advances, in orphan diseases, in inborn errors of metabolism and in global regulatory changes and experiences from Europe and Japan, as well as insights into device development. Critical new additions on pharmacogenomics and pharmacometrics have supplemented the Clinical Pharmacology section within this second edition, which has also attempted to provide the foundation of knowledge for effective global pediatric drug development written by experts.

It is with great pride and satisfaction that I thank my Associate Editors, Dianne Murphy, Julia Dunne and Lisa Mathis, who are well renowned for their expertise in pediatric drug development, for their contributions and work ethic. It is humbling to work with people who have for years demonstrated to us all their tireless energy, motivation and shared passion for the work that we do on behalf of the children of this world. Each, in her own right, has been a distinguished, well-known partner in global pediatric drug development, and also expert in helping to refine concepts that have facilitated drug development for children in the US and globally over the years. Their partnership was critical to the success of this second edition and I give my heartfelt thanks. Jon Peacock, our Development Editor at Wiley, has been patient and rigorous in his pursuit of a great second edition with us. I thank my own children, Nathaniel and Rebecca (Bekah) and my wife, Elyse, for the blessings of their love and support always of my “projects”.

Thomas Friedman, noted author, has cited that the world is becoming smaller, and he has written that the “world is flat”. Despite his advocacy of globalization in the 21st century focusing on global markets, we, as contributors to pediatric drug
development, also deal with global issues affecting children. As experts in pediatrics across the world, we are required to protect – and to voice the needs of the world’s children, speaking with one voice, whether it be in French, Japanese or English or some other language. Stakeholders involved in drug development, including academia, industry and the FDA and other regulatory agencies, must strive and continue to develop plans and actions that collaboratively and proactively benefit public health affecting children. The goal of development and facilitation of reaching these milestones is mutually important for all stakeholders, and especially for the children of the world.

Dr. Seuss (Theodor Geisel) said: “Will you succeed? Yes, you will indeed! Ninety-eight and three quarters percent guaranteed.” I believe that we are well on our way and we can aim for that final one and a quarter percent with this second edition.

The views expressed in this book are of the Editors. No official endorsement by the US Food and Drug Administration is provided or to be inferred.

Thank you.

Andrew E. Mulberg, MD, FAAP
Principal Editor
Pediatric Drug Development: Concepts and Applications,
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Cherry Hill, New Jersey
PART I
Past, Present, and Future of Pediatric Drug Development
CHAPTER 1
Introduction: Pediatric Drug Development and Therapeutics: Continued Progress for Better Drugs for Children

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While it has been less than four years since the publication of the first edition of this book, pediatric drug development has advanced dramatically in a global manner. Science in the area of pediatric drug development has advanced exponentially because of legislative incentives and requirements directed towards the development of studies of medications for use in the pediatric population [1–5]. This process has been facilitated, when appropriate, by the ability to maximize the use of data from adults and other pediatric populations to extrapolate efficacy, so that only pharmacokinetic or dynamic studies and safety assessments are required in the pediatric population [6]. Preclinical studies, which now may include juvenile animal models as needed, are conducted to ensure that there is sufficient safety information available to begin studies in children.

Children have unique vulnerabilities, as they are in an evolving process of continuing to grow and develop. Juvenile animal models have been developed and data from these studies, combined with existing data from adults and limited clinical pharmacology studies in pediatrics, have resulted in significant advances in modeling and simulations. These methods have reduced the burden of the necessity for children to be involved in clinical studies. This approach not only results in the efficient use of resources, but also provides an ethical advantage by limiting children’s exposure to clinical trials and decreasing the time it may take for a medication to be labeled with data on use in the appropriate pediatric population.

The advances made in nonclinical studies, modeling and simulation do not eliminate the need for clinical trials in pediatrics. There are still many challenges, such as the development of meaningful endpoints that can be applied across nations and cultures. This is necessary when one considers the need for studies to be multinational in order to enroll a sufficient number of patients to assess adequately the safety and efficacy of a medication. This fact is illustrated by the studies of fosinopril for the treatment of hypertension. The trials conducted to support the marketing application in the adult population enrolled 220 patients in nine US centers.
over five months, while the pediatric trials required 70 study sites in three countries over a period of 12 months in order to enroll approximately the same number of patients (253 patients) to support safety and efficacy.

According to the National Health Interview Survey performed in 2009, more than 9.5 million children in the United States had a health problem for which prescription medication had been taken regularly for at least three months [7]. It is difficult to tell if medication use in pediatrics is increasing overall, but we do know that utilization trends are dynamic in this population [8]. Although it is estimated that the pediatric population accounts for less than 10% of all medication use in the United States, pediatric patients who need medications to treat illness and/or conditions should have access to medications that have been adequately studied for use in children.

However, although there have been striking advances in some areas, there is still much that needs to be learned. Pediatric drug development has experienced dramatic advances in the last two decades. The number of medications labeled for use in the pediatric population has increased from approximately 25% to approximately 50% [9]. While this is an obvious gain, it should not be forgotten that this important work needs to continue, given that approximately half of medications still lack evidence-based information on use in children.

The recent Institute of Medicine report, Safe and Effective Medicines for Children: Studies Conducted Under the Best Pharmaceuticals for Children Act and the Pediatric Research Equity Act, documents that “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” [10]. 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, as well as 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.

In order to achieve this goal, as set out by the IOM, to recruit sick neonates and pediatric subjects in clinical trials, there are certain operational realities. The IOM states, “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” [10]. This can only be accomplished with mutual responsibility and partnership, with FDA focusing on the role of academics and private practitioners to facilitate pediatric drug development. Integration of public/private partnerships in collaboration with regulatory agencies should be a pathway for expediting and achieving some of the scientific advancements necessary to reach the goal of sound global scientific pediatric drug development programs.

Another area of dramatic change has been the globalization of pediatric studies and the implementation of the European regulations which require pediatric studies when a product is to be utilized in the pediatric population. Both the FDA and the European Medicines Agency have committed to sharing regulatory information on a regular basis in order to protect children from becoming a global commodity, and also to ensure that the best pediatric questions are being addressed by pediatric product development trials.

The FDA and the National Institutes of Health are working with organizations such as the American Academy of Pediatrics, the FDA Advisory Committees and academia. The goal is to ensure that children are protected in the course of research, that only qualified investigators are involved in studies with children, and that the best available study design and analytic methods are applied to answer the important questions that will shape pediatric therapeutics in the future.

Additional information is available at www.fda.gov/cder/pediatric/index.htm or www.fda.gov/ScienceResearch/SpecialTopics/PediatricTherapeuticsResearch/default.htm
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CHAPTER 2
History of Children and the Development of Regulations at the FDA

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2.1 Introduction and early history

Children have played pivotal roles in the development of regulations and laws to ensure that medications are both safe and effective. Efforts to protect children from dangerous or adulterated drugs are interwoven with the development of governmental protections of the larger population. Although legislative and policy efforts to protect children began decades ago, these efforts sometimes led to unintended consequences that failed to provide the expected outcomes. The history of these efforts identifies the origins of impediments and successes in pediatric studies that inform future efforts to protect children through drug therapy grounded in adequate and well-controlled studies.

With the FDA Modernization Act of 1997, voluntary studies of drugs in the pediatric population began to increase, and these have been complemented with the requirement to study new drugs in pediatric patients through the Pediatric Research Equity Acts of 2003, 2007 and 2012. These variably successful efforts to protect children from harmful products highlights the achievements of these more recent regulatory efforts and help to inform future measures to stimulate pediatric studies of drugs.

2.1.1 A civics lesson that most of us have forgotten

When the United States was founded in the 18th century, the federal system attempted to balance the rights and responsibilities of states with those of the central government. The federal government itself had several components to balance each other, with each having a core function. The Legislative Branch, consisting of two parts, establishes federal law in the context of the United States Constitution. The Executive Branch, through the Office of the President, has veto power over new laws, although that can be overridden. The Executive Branch, however, primarily implements the law through the development of policy and the issuance of regulations. Federal law invests the Executive Branch with the authority to issue regulations.

While law is developed directly through the elected representatives, regulations are developed by technical experts guided by political appointees of the Executive Branch. The purposes of the regulations are to provide additional rights or constraints and to allocate responsibilities. Regulations are intended to facilitate outcomes that may not otherwise occur, and to prevent outcomes that may otherwise occur. Regulations must be based on laws, and the underlying law or laws are always cited in federal regulations.
The Supreme Court rules on the acceptability of law, if requested, based on current interpretation of the Constitution. Lower courts, if requested, have the authority to determine the acceptability of regulations issued by the Executive Branch.

During the 19th century, only men could vote, children were considered property and anyone could sell any product for which they could find a buyer. As reading became more prevalent and printed media became more accessible, stories that captured public attention were used to influence the political process in the United States.

At that time, “medicinal products” could be made by anyone and sold for whatever use the originator claimed, although the usual ulterior motive was monetary. Attempts to regulate the manufacture and sale of food and medicinal products during the 19th century never resulted in a federal law. Debates about the balance between free enterprise and protections were never settled.

It was not until the 20th century that several widely reported scandals affecting children, with examples in the following paragraphs, resulted in the establishment of a legal and regulatory framework that addressed the basic principles of product labeling, safety, efficacy and justice. The extension of these principles specifically to address the health needs of children continued into the 21st century.

The emergence of immunotherapy, to prevent infectious diseases, in Europe in the late 19th century stimulated similar efforts in the United States. In the autumn of 1901 in St. Louis, about twenty children died after receiving horse anti-serum that was contaminated with tetanus toxin. This incident was reported widely and proved to be the essential event to persuade the United States Congress to enact the Biologics Control Act of 1902 to require the safety and purity of biologics intended for human use.

Similar media reports, published in 1905 about medicinal products harming children, resulted in the Pure Food and Drug Act in June 1906, which prohibited interstate commerce for products that were not properly labeled, were adulterated, were misbranded or which failed to conform to manufacturing standards. The law had a provision that deviation from manufacturing standards was permitted if the deviations were stated in the product label. Enforcement was through the court system, meaning that anyone challenging a manufacturer would need to file a suit. In 1911, the Supreme Court ruled in the case of the United States vs. Johnson that the law only extended to false and misleading statements regarding the ingredients and did not extend to any claims about the use of the product. Not accepting the outcome of this ruling, Congress enacted in 1911 the Sherley amendment, which extended the authority of the federal government to prosecute false or misleading therapeutic claims, but only in the circumstance where intent to fraud could be established.

The legal authority for the Biologics Control Act and the Pure Food and Drug Act was provided in the authority of the government to regulate products intended for interstate commerce. If a product was produced and used locally, then regulatory authority could only come from state or local authorities.

In 1909, President Theodore Roosevelt presided over the first White House Conference on the Care of Dependent Children. This was in response to a telegram he had received on behalf of social activists, posing the question that if the Secretary of Agriculture was touring the South to understand what the boll weevil was doing to cotton crops, should not the federal government gather the facts regarding why so many children die of infections during the summer. This conference led to the establishment in 1912 of the United States Children’s Bureau to coordinate federal policy for children. The Bureau became the primary fact-gathering facility for the status of children for the federal government and was within the Social Security Administration before becoming part of the Department of Health and Human Services under the Administration for Children and Families.

The 1930s established the National Institutes of Health, the Food, Drug and Insecticide Administration (subsequently shortened to the Food and Drug Administration or FDA) and a new law triggered by another tragedy involving children. A chemical company substituted diethylene glycol for ethanol in the manufacture of sulfanilamide, a broad
spectrum antibiotic, to improve its solubility in an effort to produce a liquid that could be administered to children. Subsequently, about 100 people died from ingesting this liquid form of the medication. The product was labeled as an elixir, which at the time meant containing ethanol, so the company was prosecuted for misbranding but had no legal responsibility for any of the deaths.

In response to these deaths, the Food, Drug and Cosmetic Act became law in 1938. This Act required safety to be established prior to marketing, disclosure of all active ingredients, directions for use and warnings about misuse unless the product was sold by prescription. It allowed federal inspections of manufacturing facilities, established procedures for the formal review of applications for marketing, explicitly prohibited false claims and extended the scope to cosmetics and devices.

In the early 1960s, the birth of children with multiple malformations related to pregnant women taking the sedative thalidomide led to the Kefauver-Harris Amendment to the Food, Drug and Cosmetic Act. This amendment extended FDA oversight of medications and required a demonstration of efficacy prior to approval of a marketing claim. Additional provisions in the amendment were the need to establish good manufacturing practice (GMP) and maintain production records, the requirement to file an application with the FDA prior to clinical testing (Investigational New Drug application, or IND), an increase in the time for FDA marketing authorization review from 60 to 180 days, the transfer of regulatory authority for drug advertising to the FDA, and the authority to withdraw marketing approval if new evidence indicated lack of safety or effectiveness.

The mechanism of an Investigational New Drug (IND) application is based on two principles. The first is that products may not be used for interstate commerce unless a federal license is granted in the form of marketing authorization. An exception is made for the period of time when a product is under development and is to be tested in humans, based on a request by a product developer to receive an IND. The second principle is that the FDA provides review and oversight for the product development process.

Based on both the new legal requirement for premarketing review of products and a series of scholarly articles documenting human subject research practices that were perceived as exploitative and even abusive, the US Public Health service issued a memo in 1966 requiring all institutions receiving federal funds to establish independent review of proposed human subject research. In 1974, Congress passed the National Research Act, expanding the scope of human subject research review for federally funded projects but allowing each agency to set its own policies and practices.

The National Research Act also established a Commission for the Protection of Human Subjects of Medical and Behavioral Research. The National Commission held hearings and began to issue recommendations. The first recommendations came in 1976 for research enrolling prisoners, and the second set came in 1977 for research enrolling children. The National Commission noted two fundamental principles. The first is that children are different from animals and adults, and thus it is necessary to generate data about children from studies in children. The second principle is that the greatest risk of harm from the use of therapeutics is not to have relevant research.

The National Commission classified research into levels of risk, establishing the concept of minimal risk and differentiating acceptable research into minimal risk and a minor increase over minimal risk but with expected benefits. The benefits may accrue directly to the individual research participant, or to others with similar conditions. In either case, the potential benefits must justify the potential risks in order for the research to proceed.

The National Commission issued a report in 1979 known as the Belmont Report. This stated three principles:

1. Respect for the personal dignity and autonomy of individuals, with special protections for those with diminished autonomy.
2. Beneficence to maximize benefit and to minimize harm.
3. Justice to distribute fairly and equitably the benefits and burdens of research.

In 1983 the recommendations of the Commission were adapted to become federal regulations.
At the American Academy of Pediatrics (AAP) annual meeting in 1972, Dr. Charles Edwards, former FDA Commissioner, stated that the large majority of medications used in infants and children were prescribed on an empiric basis and lacked sufficient evidence of safety and effectiveness. In 1974, the AAP issued a report commissioned by the FDA called *General Guidelines for the Evaluation of Drugs to Be Approved for Use during Pregnancy and, for the Treatment of Infants and Children*. This was echoed in the 1977 American Academy of Pediatrics Committee on Drugs policy statement that, “it is not only ethical but also imperative that new drugs to be used in children be studied in children . . . so the benefits of therapeutic advances will become available to all who may need them.”

In 1977, the FDA adopted the AAP report as a guidance document. A guidance document, unlike a law or regulation, is not legally binding. It represents a default recommendation, but alternative options may be implemented. Also in 1977, the AAP issued *Guidelines for the Ethical Conduct of Studies to Evaluate Drugs in Pediatric Populations*. The major points were:

- An emphasis on unexpected toxicities.
- Reasonable evidence for efficacy should exist prior to study in infants and children.
- Sick children should be enrolled in studies.
- Active or historical controls preferred over placebo.
- Decreasing age order for study enrollment.

### 2.2 Product label changes

A Product Package Insert for a specific drug product, often referred to as the label, as described in the Code of Federal Regulations (CFR) Title 21 Part 201, contains the following sections:

- Description
- Clinical pharmacology
- Indications and usage
- Contraindications
- Warnings
- Precautions
- Adverse reactions
- Drug abuse and dependence
- Overdosage
- Dosage and administration
- How supplied.

General labeling principles are that:

- The labeling shall contain a summary of the essential scientific information needed for the safe and effective use of the drug.
- The labeling shall be informative and accurate, and neither promotional in tone nor false or misleading in any particular.
- The labeling shall be based, whenever possible, on data derived from human experience. Conclusions based on animal data, but necessary for safe and effective use of the drug in humans, shall be identified as such and included with human data in the appropriate section of the labeling.

The Code of Federal Regulations Part 201 Subpart B section 201.57(c)(iv) notes, “If there is a common belief that the drug may be effective for a certain use or if there is a common use of the drug for a condition, but the preponderance of evidence related to the use or condition shows that the drug is ineffective, the Food and Drug Administration may require that the labeling state that there is a lack of evidence that the drug is effective for that use or condition”.

In 1979, the FDA published a regulation establishing a Pediatric Use Subsection in the Precautions Section of Product Package Inserts (21 CFR 201.57 (f)(9)). This regulation stated that, in the absence of substantial evidence for any pediatric population, the label shall state, “Safety and effectiveness in pediatric patients have not been established”.

If use of the drug in premature or neonatal infants, or other pediatric subgroups, is associated with a specific hazard, the hazard shall be described in this subsection of the labeling or, if appropriate, the hazard shall be stated in the “Contraindications” or “Warnings” section of the labeling and this subsection shall refer to it.

If a sponsor believes that none of the above apply, alternate wording may be proposed.

If the drug product contains one or more inactive ingredients that present an increased risk of toxic effects to neonates or other pediatric subgroups, a special note of this risk shall be made,
generally in the “Contraindications”, “Warnings” or “Precautions” section.

Although this legislation was well intended and did create a specific place for pediatric information, that information was usually that “Safety and effectiveness in pediatric patients have not been established”. Over time, this statement was not thought to be useful, as studies could have been conducted but failed to demonstrate efficacy. However, none of that information was available as it was considered Commercial Confidential information. As so few pediatric studies were being performed, any form of information garnered from such studies was considered to be of public health interest.

This issue of the need for access to the information from pediatric studies was addressed in later legislation. Later legislation also removed Pediatrics as a “Caution” and placed pediatric information in section 8.4.

The year 1983 was notable not only for the publication of the federal Human Subject Protection regulations but also for the establishment of the Orphan Drug Act, which established the principle that incentives, in this case a longer period of exclusivity following marketing authorization and monetary support through grants for premarketing development, can be used by the federal government to address underserved populations with diseases that have a prevalence of less than 200,000.

2.3 FDA pediatric initiatives with voluntary compliance

By the mid-1990s, the FDA had established regulatory tools to facilitate product labeling for pediatric use on a voluntary base. In 1994 the FDA added a subsection to the Pediatric Use section of the product label, allowing the use of extrapolation of efficacy from adults to children in certain circumstances to decrease the evidence burden for pediatric labeling (21 CFR 201.57(f)(9) with added subsection (iv)).

In 1997, the path to pediatric labeling gained an important tool based on the Orphan Product model. Section 111 of the Food and Drug Administration Modernization Act (FDAMA) extended the incentive opportunity for most drugs, from those restricted to rare diseases to include any intended indication that used the active moiety if the sponsor performed pediatric studies. To maintain public health relevance and quality control over which pediatric studies were performed, the program provided the FDA with a gatekeeper function in that the pediatric data could only be granted an incentive if the FDA asked for the information with a Pediatric Written Request (see Figure 2.1).

The requested information did not need to demonstrate efficacy, result in a new pediatric indication or even change the label, but the studies did have to provide credible data that would address knowledge gaps, based on FDA’s assessment, in pediatric use. The incentive was a lengthening by six months of either the intellectual property protection from a patent granted to the product by the Patent and Trademark Office of the US Department of Commerce or the marketing exclusivity license granted by the FDA. The incentives are summarized in Table 2.1.

Some differences between patent protection and exclusivity are worth noting to understand the incentive program. The concept of patents is based in Article I, Section 8, Clause 8 of the United States Constitution, noting that “The Congress shall have power . . . to promote the progress of science and useful arts, by securing for limited times to authors and inventors the exclusive right to their respective writings and discoveries . . . ” The legal basis is the Patent Act of 1952, codified in Title 35 of the United States Code. A patent is granted for an initial period of 20 years, and it is the responsibility of the patent holder to protect the intellectual property through the court system. Due to the general practice of patenting candidate drugs early in the product development cycle, a substantial portion of the patent duration may have elapsed by the time a product receives an FDA license for marketing. If a patent holder can demonstrate that marketing was reduced by regulatory delays, the patent holder can file for an extension up to five years.

Pediatric exclusivity is different than the usual exclusivity that FDA grants, and is a powerful incentive. Usually, exclusivity is an exclusive
marketing license granted by the FDA for the sale of an approved form of a specific product, for a specific approved use of the product for interstate commerce. What is protected is the approved use of a particular product, not the product itself independent of use. Marketing exclusivity is granted with the provision that the FDA will not grant another license to anyone else for the same product for the same use for a fixed period of time. For marketing exclusivity, it is the federal government that takes responsibility for protection. While marketing exclusivity is for the combination of a particular form of a product and its approved use, the pediatric incentive can apply to any approved use of any form of the product that uses what is termed the active moiety. Simply put, all forms of the product with the active moiety now have six months of additional marketing exclusivity.

Following a successful five-year initial experience as part of the 1997 FDAMA, with 49 products receiving pediatric exclusivity, the incentive program became a law in 2002 as the Best Pharmaceuticals for Children Act for another five years.

In addition, The Best Pharmaceuticals for Children Act (BPCA) of 2002:

- required a review of safety by an external advisory committee for all products granted exclusivity

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**Figure 2.1** FDA Pediatric Written Request process.

**Table 2.1** Pediatric incentives available through FDAMA.

<table>
<thead>
<tr>
<th>Type of protection</th>
<th>Initial protection, years</th>
<th>Protection with pediatric incentive, years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patent protection for intellectual property</td>
<td>20</td>
<td>20.5</td>
</tr>
<tr>
<td>Initial indication for a new drug</td>
<td>5</td>
<td>5.5</td>
</tr>
<tr>
<td>Supplemental indication for a marketed drug</td>
<td>3</td>
<td>3.5</td>
</tr>
<tr>
<td>Orphan indication for a drug</td>
<td>7</td>
<td>7.5</td>
</tr>
</tbody>
</table>
(see PREA for establishment of the Pediatric Advisory Committee);
• created the Office of Pediatric Therapeutics in the Office of the Commissioner and required that office to have an ethicist;
• assigned a role for the National Institutes of Health, and specifically the National Institute for Child Health and Human Development (NICHD), to administer a program for products that would require further pediatric studies if:
  o there is no interest on the part of the sponsor for a product with patent protection or FDA issued exclusivity;
  o a product that has no exclusivity or patent protection to which an exclusivity extension can be appended (the latter case applies to off patent and generic medications);
  o the NICHD and the FDA develop a priority list of products that require further information;
• publication on the FDA website of summaries of the clinical, pharmacology and statistical reviews of pediatric studies.

2.4 Initial pediatric mandate

To complement the voluntary programs, the FDA issued a regulation in 1998 requiring pediatric development of a product if the adult condition for which a product was licensed had a relevant pediatric population, and if the product was likely to be used in children due to either a meaningful therapeutic advance over existing therapy or if widespread use was anticipated. Widespread use was calculated to be greater than 50,000 children with the disease or condition, based on the assumption that the threshold for orphan designation was prevalence less than 200,000 and children were about 25% of the population.

Compliance could be deferred so that availability to the adult population would not be delayed. Waivers from compliance were also part of the program in cases where pediatric studies would not be feasible, or where the product was not a therapeutic advance compared to existing products, or the licensed indication was a condition that did not exist in children.

The program was challenged in a court of law on the grounds that, if a manufacturer did not intend for a product to be used in children, the federal government lacked authority to compel pediatric development. The challenge was upheld, which stopped implementation of the regulation.

The authority was then granted by Congress and signed into law in 2003 in the Pediatric Research Equity Act. Similar to its predecessor, the 1998 Pediatric Rule, the Pediatric Research Equity Act (PREA) provided a mandate that covered all drugs and biologics and established a standing FDA Pediatric Advisory Committee.

An algorithm for the application of PREA is shown in Figure 2.2.

2.5 Additional protections for children participating in studies

The institutionalization of federal pediatric initiatives led the FDA to anticipate significant increases in the number of pediatric studies and in the number of children enrolled in studies. To ensure adequate protection, the FDA organized a Pediatric Advisory Subcommittee meeting in 2000 to discuss enrollment of children in research. The outcome of the meeting was a recommendation that only children with a disease or condition or with a high likelihood of becoming a patient with a disease or condition should be enrolled in studies. An example of high likelihood would be a toddler in a day care setting experiencing a middle ear infection or an upper respiratory infection.

The Committee and the American Academy of Pediatrics recommended that FDA adopt the protections offered under the Common Rule and, in particular, Subpart D, for children who are in studies using FDA regulated products. The original Common Rule and Subpart D applied only to federally funded research but, with the expectation that many pediatric studies would now be funded by non-federal sources, additional protections were needed. The FDA interim adaptation of the Common Rule and Subpart D are published in the Code of Federal Regulations Title 21 Part 50. Final adoption of Subpart D in FDA regulations is expected soon.
2.6 Federal pediatric initiatives – first decade experience

Over the first decade of the incentive program and mandate program, about 250 products received pediatric use information in the package insert or label.

An NIH analysis of the resource expectations for generating data in response to a Written Request showed that, for studies that were solely for pharmacokinetics, the average study size across a portfolio of 195 individual studies that covered a range of 73 conditions.

Table 2.2 Comparison of major features of US Pediatric Initiative Programs.

<table>
<thead>
<tr>
<th>US Pediatric Mandate Program (PREA)</th>
<th>US Pediatric Incentive Program (BPCA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Applies to all drugs and biologicals except orphan designation</td>
<td>Biologicals and some drugs excluded but includes orphan designation</td>
</tr>
<tr>
<td>Only applies to the drug product and indication under review</td>
<td>Applies to all products with same active moiety</td>
</tr>
<tr>
<td>Only applies if an approved or pending indication occurs in adults and children</td>
<td>Eligible indications for study must occur in pediatric populations</td>
</tr>
<tr>
<td>Only applies if there is a meaningful therapeutic advance or widespread use</td>
<td>Only applies when there is underlying patent or exclusivity protection and meets the terms of providing a health benefit</td>
</tr>
<tr>
<td>Mandatory – compliance expected</td>
<td>Voluntary – no compliance expected</td>
</tr>
<tr>
<td>May be used as often as public health need arises</td>
<td>May only be used once in a product lifetime</td>
</tr>
</tbody>
</table>

(b) Market exclusivity for new drugs:
(1) In general: except as provided in paragraph (2), if, prior to approval of an application that is submitted under section 505(b)(1), the Secretary determines that information relating to the use of a new drug in the pediatric population may produce health benefits in that population, the Secretary makes a written request for pediatric studies.
drug products in 33 drug classes in 12 disease categories was related to the study goals. A pharmacokinetic (PK) study examined only PK parameters. A pharmacodynamics (PD) study examined biological, physiological or clinical responses, often as a proof of concept of activity. Some studies combined both pharmacokinetics and pharmacodynamics to determine biologically active dose ranges. Efficacy studies are defined as studies that are sufficiently powered statistically to establish clinical benefit.

Table 2.3 summarizes the average study size based on the number of patients enrolled and the goals of the study.

### Table 2.3 Average study size and study goals.

<table>
<thead>
<tr>
<th>Study type</th>
<th>PK</th>
<th>PK-PD</th>
<th>PD</th>
<th>Efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average number of participants</td>
<td>33</td>
<td>68</td>
<td>157</td>
<td>249</td>
</tr>
</tbody>
</table>

2.7 Food and drug administration act of 2007 – third generation of pediatric initiatives

The Food and Drug Administration Act of 2007, referred to as FDAAA, had three sections devoted to pediatric initiatives. Title IV was the reauthorization of the Pediatric Research Equity Act and Title V was the reauthorization of the Best Pharmaceuticals for Children Act. A new initiative, Title III, the Pediatric Medical Device Safety and Improvement Act, was directed to medical devices but did not contain an incentive program. A summary of the key components of the FDAAA are:

- **Title III: Pediatric Medical Device Safety and Improvement Act of 2007:**
  - Requires that an application for a device must include a description of any pediatric subpopulations that suffer from the condition that the device will treat, diagnose or cure
  - Requires the Secretary to submit a plan for expanding pediatric medical device research and development to the US Congress
  - Definition of pediatric as through age 21 years. *Note that the labeling regulations for drug products define pediatric as through 16 years.*

- **Title IV: Pediatric Research Equity Act of 2007:**
  - Sets forth conditions under which the Secretary may grant waivers or deferrals of requirements that applicants submit as a pediatric assessment for new drugs and biological products
  - Permits the Secretary to require the sponsor of drug application to submit an assessment of the effect of the product in pediatric populations
  - Requires the Secretary to use an internal committee to review all pediatric plans and waivers prior to approval of an application
  - By 2010, requires the Secretary to contract with the Institute of Medicine to conduct a study on pediatric studies conducted in response to BPCA and PREA
  - Requires inclusion of negative information in the product label
  - Posting of full reviews of pediatric data reviews on the FDA web site.

- **Title V: Best Pharmaceuticals for Children Act of 2007:**
  - Requires the Secretary to use an internal committee to review all pediatric plans
  - Permits the Secretary to request the holder of a drug application to conduct pediatric studies if it is determined that the new drug may produce health benefits in the pediatric population
  - Posting of text of Written Requests when product data are submitted
  - Requires inclusion of negative information in the product label.
  - Requires development of a Priority List based on conditions that require additional therapeutic options, particularly those with no acceptable options. *Note the Priority List previously was based on identifying individual products with data gaps on pediatric use.*

The results of the pediatric initiatives over the first dozen years were robust, with a total of about 200 products granted pediatric exclusivity and