PEDIATRIC NON-CLINICAL DRUG TESTING

PRINCIPLES, REQUIREMENTS, AND PRACTICES

EDITED BY
ALAN M. HOBERMAN
ELISE M. LEWIS

WILEY

Pediatric Nonclinical Drug Testing

Pediatric Nonclinical Drug Testing

Principles, Requirements, and Practices

Edited by

Alan M. Hoberman, PhD, DABT, Fellow ATS
Elise M. Lewis, PhD

A JOHN WILEY & SONS, INC., PUBLICATION

Published by John Wiley & Sons, Inc., Hoboken, New Jersey
Published simultaneously in Canada

Library of Congress Cataloging-in-Publication Data:

Pediatric non-clinical drug testing : principles, requirements, and practice
/ edited by Alan M. Hoberman, Elise M. Lewis.
p. ; cm.
Includes bibliographical references.
ISBN 978-0-470-44861-8 (cloth)
I. Hoberman, Alan M. II. Lewis, Elise M.
[DNLM: 1. Drug Evaluation, Preclinical–United States. 2. Age Factors–United States. 3. Child–United States. 4. Drug Approval–United States. 5. Drug Toxicity–prevention & control–United States. 6. Infant–United States. 7. Models, Animal–United States. QV 771]
615.7'040287–dc23
2011043323

Printed in the United States of America

10 9 8 7 6 5 4 3 2 1

The editors and authors dedicate this book to the memory of Mildred S. Christian (1942–2009). She worked tirelessly in the field of reproductive and developmental toxicology to ensure the health of the fetus and the newborn, a very special population that needs special protection. This book represents her vision to bring nonclinical pediatric research to the next level, protecting the health of the child. It is a tribute to her lifetime of research and dedication to regulatory science.

Mildred Stoehr Christian, Ph.D., Fellow ATS, began her career when teratology and reproductive and developmental toxicology were just beginning to emerge as important fields of regulatory research. In response to this challenge, Dr Christian founded Argus Research Laboratories in 1979 to investigate the safety and evaluate the risk of drugs and chemicals to the conceptus. Shortly afterward, she established Argus International and a team of consultants to fill the need to provide expert opinions on data generated to protect the unborn, while allowing for the use of a drug or chemical to cure a disease or promote general health. Dr Christian became a regulatory expert through her active participation as an advisor to US and international agencies, including the FDA, EPA, OECD, and ICH.

As the pool of research grew, it became increasingly obvious that the protection she was trying to provide to children in utero needed to be extended to the newborn and to the growth and development of children. In response to this challenge, she began attending and participating in conferences, symposia, and workshops on juvenile toxicity testing. Dr Christian assembled some of the finest experts in the field of toxicity testing and risk evaluation to address how to conduct nonclinical research for juvenile patients. Through the diligent efforts of Dr Christian, the contributing authors agreed, the publisher was interested, and so began the compilation of this book.

Throughout her long career, Dr Christian tirelessly shared her knowledge through presentations at seminars, scientific meetings, workshops, and courses. She was actively involved in many professional organizations and societies and held numerous offices and chairmanships. She authored over 120 papers and book chapters and was the founder and editor (for 10 years) of *The Journal of the American College of Toxicology* (now *International Journal of Toxicology*).

On March 26, 2009, Dr Christian lost her battle with cancer, leaving behind a long legacy and an unfinished book as her final gift. Her colleagues were so committed to her vision and ideas surrounding this publication that they decided to finish it as a tribute to her contributions to a safer world.

Contents

Preface

Nonclinical pediatric testing is a "hot topic." This text is solely dedicated to pediatric testing and targets the specific needs and effects associated with juvenile test animals and, ultimately, juvenile humans. It not only covers the actual aspects of testing but also deals with the associated clinical and regulatory aspects that require updating in this rapidly changing area.

The information collected from international sources and contained herein would benefit all scientific and regulatory people associated with drug development or safety testing of drugs.

This book will prove valuable to international regulatory personnel, in understanding and referencing appropriate designs and concerns; to toxicologists and pharmacokinetics personnel working in industrial, academic, and clinical settings; to regulatory affairs personnel, regarding submission of dossiers; and to physicians involved in safety considerations regarding treatment of children with pharmaceuticals.

This single book will provide the major reference that will be used to obtain historical experience, appropriate rationales for developing the pediatric investigational plan (PIP), and appropriate methods for selection of species and study designs for conducting the necessary pediatric evaluations in animals.

The primary market includes toxicologists, teratologists, developmental neurotoxicologists, and pharmacokineticists who generally have Ph.D. degrees and attend meetings such as the Society of Toxicology, American College of Toxicology, Teratology Society, European Toxicology Society, European Teratology Society, the Japanese Toxicology Society, and the Japanese Teratology Society. A secondary market includes the regulatory affairs professional, who is responsible for interacting with the toxicologists in developing the regulatory submissions.

The professionals are generally BS- and Ph.D.-level personnel working in pharmaceutical companies, CROs, and various international regulatory bodies. Their primary meetings are those associated with the Drug Information Association (DIA), an international society dedicated to bringing information to the regulatory community. The tertiary market is the academic toxicology and pediatric medical communities, where this book could be used as a textbook for toxicology and pediatric medicine courses.

Although nonclinical and clinical testing needs for drugs for pediatric populations have been discussed for more 40 years, ethical, political, and practical issues continue to plague pediatric testing and labeling. A new European regulation on pediatric medicines became mandatory for the European Medicines Agency (EMA) in 2008. This book describes the practical issues regarding nonclinical testing to meet FDA guidelines, differences resulting from the new EMA legislation, and ways to develop appropriate information for submission to both agencies, as well as provides practical study designs and approaches that can be used to meet international requirements. It focuses on considerations regarding nonclinical testing models, including (i) lack of fully comparable models, and how to address these problems; (ii) inadequate historical experience, and provides examples of current historical experience with multiple species; and (iii) practical difficulties in using the clinical route of exposure in the animal model, and provides information on how to overcome these problems.

Several books and manuscripts exist that include chapters on pediatric testing requirements and responses of specific organ systems, but these do not address the most recent EMA requirement, which are relevant to all applications to the EMA and which will be shared on a monthly basis with the FDA, specifically, the PIP, which will be addressed in this document. Similarly, none of them include historical control information for multiple species in a single compendium.

Acknowledgments

The editors gratefully acknowledge all the assistance given to the individual authors in compiling this book. Contributors have chosen to personally thank these people and organizations, without whose valuable assistance, this book would not have been compiled and published in their own chapters.

Contributors

PIETER P. ANNAERT, Department of Pharmaceutical Sciences, Katholieke Universtiteit Leuven, Leuven, Belgium

GRAHAM P. BAILEY, Toxicology/Pathology - Global Preclinical Development J&J Pharmaceutical Research and Development, Division of Janssen, Beerse, Belgium

JOHN F. BARNETT, Neurobehavioral Toxicology Department, Charles River Laboratories Preclinical Services, Horsham, PA

PAUL C. BARROW, CiToxLAB, Evreux Cedex, France

KIMBERLY C. BRANNEN, Reproductive Toxicology, Charles River Laboratories Preclinical Services, Horsham, PA

GARY J. CHELLMAN, Developmental and Reproductive Toxicology, Charles River Laboratories, Preclinical Services, Reno, NV

TIMOTHY P. COOGAN, Biologics Toxicology, Centocor Research & Development, Inc, Radnor, PA

LUC M. DE SCHAEPDRIJVER, Toxicology/Pathology Global Preclinical Development, Janssen R&D, a division of Janssen Pharmaceutica NV, Beerse, Belgium

LOECKIE L. DE ZWART, Drug Metabolism and Pharmacokinetics—Global Preclinical Development, J & J Pharmaceutical Research & Development, Beerse, Belgium

NIELS-CHRISTIAN GANDERUP, Ellegaard Göttingen Minipigs, Dalmose, Denmark

ALAN M. HOBERMAN, Research Department, Charles River Laboratories Preclinical Services, Horsham, PA

FRIEKE KUPER, TNO Quality of Life, Zeist, Netherlands

SUSAN B. LAFFAN, Safety Assessment Reproductive Toxicology, GlaxoSmithKline, King of Prussia, PA

ELISE M. LEWIS, Reproductive and Neurobehavioral Toxicology, Charles River Preclinical Services, Horsham, PA

BEATRIZ SILVA LIMA, EMA Pediatrics Committee Chair and University of Lisbon, Lisbon, Portugal

SUSAN L. MAKRIS, EPA Office of Research and Development, National Center for Environmental Assessment, Washington, DC

JOHAN G. MONBALIU, Drug Metabolism and Pharmacokinetics—Global Preclinical Development, J & J Pharmaceutical Research & Development, Beerse, Belgium

ROBERT E. OSTERBERG, Aclairo Pharmaceutical Development Group Inc, Vienna, VA

ANDRÉ H. PENNINKS, Experimental Immunology, TNO Triskelion BV, Zeist, Netherlands

LORRAINE POSOBIEC, Safety Assessment Reproductive Toxicology, GlaxoSmithKline, King of Prussia, PA

JOSÉ RAMET, Department of Paediatrics, Universitair Ziekenhuis Antwerpen UZA, Antwerp, Belgium

ALLAN DAHL RASMUSSEN, Regulatory Toxicology and Safety Assessment, H. Lundbeck A/S, Valby, Denmark

KEITH ROBINSON, Reproductive Toxicology, Charles River Laboratories, Preclinical Services Montreal, Quebec, Canada

SUSAN Y. SMITH, Bone Research, Charles River Laboratories, Preclinical Services Montreal, Quebec, Canada,

COR J. SNEL, Reproductive Toxicology, TNO Triskelion BV, Zeist, Netherlands

BERT SUYS, Congenital and Pediatric Cardiology, University Hospital Antwerp, Belgium

GEERTJE J.D. VAN MIERLO, The Experimental Immunology Group, TNO Triskelion BV, Zeist, Netherlands

ANDRE VIAU, Inhalation Toxicology, Charles River Laboratories, Preclinical Services Montreal, Quebec, Canada

ELVIRA VOGELWEDDE, Safety Assessment, Covance Laboratories GmbH, Münster, Germany

GERHARD F. WEINBAUER, Developmental and Reproductive Toxicology, Covance Laboratories GmbH, Muenster, Germany

ANDRÉ P.M. WOLTERBEEK, Reproductive and Developmental Toxicology, TNO Triskelion BV, Zeist, Netherlands

1

Introduction

Elise M. Lewis, Luc M. De Schaepdrijver, and Timothy P. Coogan

1.1 INTRODUCTION

Children, like adults, benefit from the continuing advances in biomedical research, including the use of animal models, to evaluate the safety and efficacy of pharmaceutical products, medical devices, and biopharmaceuticals. These advances in biomedical research are central to the ongoing improvements in medical care and public health policies that are intended to prevent or lower the incidence of childhood illnesses or diseases, improve the quality of life for pediatric patients, and ultimately, save or prolong the lives of millions of children around the world. Despite these advances, the looming concern is that children do not benefit equally from these overall advances in biomedical research. This is demonstrated by the continued "off-label" use of medicines to treat childhood illnesses and diseases and the lack of investment in formulations specifically for children regardless of legislative progress [1]. This problem is illustrated by the World Health Organization (WHO) estimate that nearly 9 million children younger than 5 years and more than 1.8 million young people older than 15 years die each year and an even greater number of young people suffer from illnesses that hinder their normal growth and development [2].

To understand the full complexity of this problem, one must be aware of the various illnesses or disabilities that affect "children," a grouping that includes all individuals from preterm newborn infants to 18-year-old adolescents. As shown in Table 1.1, diseases that can occur in the pediatric population include, but are not limited to, bacterial, viral, and parasitic infections; nutritional diseases; congenital

Pediatric Nonclinical Drug Testing: Principles, Requirements, and Practices,
First Edition. Edited by Alan M. Hoberman and Elise M. Lewis.

TABLE 1.1 Disease States Observed in Children

- Bacterial infections and mycoses
- Parasitic diseases
- Musculoskeletal diseases
- Stomatognathic diseases
- Otorhinolaryngologic diseases
- Eye diseases
- Cardiovascular diseases
- Congenital, hereditary, and neonatal diseases and abnormalities
- Nutritional diseases
- Immunologic diseases
- Mental disorders
- Viral diseases
- Neoplasms
- Digestive diseases
- Respiratory tract diseases
- Nervous system diseases
- Metabolic diseases
- Hematologic and lymphatic diseases
- Skin and connective tissue diseases
- Endocrine diseases
- Disorders of environmental etiology/exposure
- Urogenital diseases

TABLE 1.2 Common Childhood Illnesses

- Candidiasis (''thrush'')
- Chicken pox
- Cystic fibrosis
- Diabetes
- Fifth disease
- Leukemia
- Mumps
- Roseola
- Tetanus
- Bowel disorders
- Chagas disease
- Croup
- Cytomegalovirus (most frequent virus transmitted before birth)
- Malaria
- Influenza
- Measles
- Rheumatic fever
- Rubella
- Whooping cough
- Febrile seizures

anomalies; cancer; or diseases of the various organ systems (e.g., immune, nervous, cardiovascular, musculoskeletal, gastrointestinal, respiratory, or urogenital). Some of the most common childhood illnesses are presented in Table 1.2. As mentioned by Crosse "Although children suffer from many of the same diseases as adults and are often treated with the same drugs, only about one-third of the drugs that are prescribed for children have been studied and labeled for pediatric use" [3].

The "off-label" use of medicines and lack of investment in pediatric formulations is not a new issue. The clinical aspect of developing, and using, therapeutic agents and surgical treatments in preadult patients has been, and continues to be, a complicated and controversial medical problem. Approximately 40 years ago, children were referred to as *therapeutic orphans* [4], a phrase that was coined by Dr. Harry Shirkey because of excessive use of the pediatric disclaimer clause (i.e., "not to be used in children, since clinical studies have been insufficient to establish recommendations for its use" [5]) in drug labels

following an amendment in 1962 to the Federal Food, Drug and Cosmetic Law [6]. The term "therapeutic orphan" remains relevant today [6,7], as it purports two ethical dilemmas that physicians are frequently challenged with: (i) depriving infants, children, or adolescents of potentially beneficial therapies because of an apparent information gap [7] and (ii) prescribing medicines on the basis of prior experience(s) and extrapolating doses on the basis of data generated in adult patients [8].

More recently, the phrase "canaries in the mineshafts" [9,10] has been applied to this vulnerable population because children "die more quickly and in greater numbers from therapeutic mishaps" [9]. These mishaps include, but are not limited to, overdosing resulting in potential toxicity or underdosing resulting in potential inefficacy [11]. Several examples that resulted in legislative changes regarding pediatric drug development are outlined in Fig. 1.1. While legislative changes are welcomed by proponents of pediatric medicine and they provide the mechanisms necessary to acquire information on pediatric safety and efficacy to improve product labeling, the overall progress throughout the industry has been slower than desired, in part, because the pediatric population represents a small market within the drug development community.

We all agree that a "child is not a small adult" [37] and children should not be considered a "homogenous category" [37]. While it is obvious that children rapidly change and develop physically, cognitively, and emotionally [8] from birth to adulthood, there are inherent kinetic differences between children and adults that could result in over- or underexposure to medicinal products. In children, growth and development can affect the process by which a drug is absorbed, distributed, metabolized, and excreted from the body. In addition, protein binding can be affected by age. Some notable differences observed in children compared to adults include (i) immaturity of the renal and hepatic clearance mechanisms; (ii) immaturity of the blood–brain barrier, higher water content, and greater surface area in the bodies of infants; (iii) unique susceptibilities observed in newborns; (iv) rapid and variable maturation of physiologic and pharmacologic processes; (v) organ functional capacity; and (vi) changes in receptor expression and function [72,73]. As noted by Brent [74], "in many instances environmental toxicants will exploit the vulnerabilities and sensitivities of developing organisms. In other instances, there will be no differences between the developing organism and the adult when exposed to toxicants, and in some instances the children and adolescents may even withstand the exposures with less insult." Examples of drugs that demonstrate different toxicities in adult and pediatric populations are summarized in Table 1.3.

Later in this book, the subject matter expert for clinical concerns addresses special considerations when treating children and differences in methods required for treatment of children and adults, including the route and formulation, selection processes for clinical trials, informed consent, and risk/benefit considerations in the treatment of children.

Year	Milestone	Reference(s)
1775	• Pott describes scrotal cancer in chimney sweeps	12
1904	• Paint dust identified as the major source of lead in children	13
1934	• Phenylketonuria discovered	14, 15, 16
1951	• Retinopathy of prematurity linked to oxygen therapy (Silverman)	17,18,19
1956	• Sulfa drugs associated with kernicterus	20
1957	• Chloramphenicol-gray baby syndrome	21, 22, 23, 24, 25
1959	• Surfactant therapy for respiratory distress	26
1966	• Wilson's principles	27
1971	• Hexachlorophene effects on rat brains reported	28, 29
1972	• Hexachlorophene human effects	30, 31, 32
1973	• Environmental Protection Agency (EPA) begins lead phase-out from gasoline	33
1974	• Congress passes National Research Act and establishes National Commission for the Protection of Human Subjects of Medical and Behavioral Research	34, 35
	• American Academy of Pediatrics (AAP) report commissioned by FDA on "General Guidelines for the Evaluation of Drugs to be Approved for Use during Pregnancy and for Treatment of Infants and Children"	36
1977	• National Commission Report on "Research Involving Children"	37
	• FDA Pediatric Guidance "General Considerations for the Clinical Evaluation of Drugs in Infants and Children"	38
	• Consumer Product Safety Commission (CPSC) bans use of lead paints in housing	39
1979	• FDA Regulation on Pediatric Use Subsection on Product Package Insert Precautions Section [21 CFR 201.57 (f)(9)]	40
1980	• Reye's syndrome linked to aspirin	41, 42, 43, 44, 45
1982	• Benyzl alcohol induces "gasping syndrome"	46
	• Cyclosporine approved for general use in US without being tested in children; later found to metabolize faster in children	47
1991	• First FIFRA developmental neurotoxicology requirement	48
1996	• Clean Air Act Amendment banned lead and lead additives in gasoline	49
	• FDA Guidance on "Content and Format of Pediatric Use Section"	50
	• Pediatric Rule revised [21 CFR 201.57 (f)(9)] with added subsection (iv) on using extrapolation as a basis for pediatric use	50
	• Food Quality and Protection Act	51
1997	• Food and Drug Administration Modernization Act (FDAMA) – initial pediatric incentive program	52
1998	• Pediatric Rule – mandated pediatric studies under particular circumstances	53
1999	• Qualifying for Pediatric Exclusivity under section 505A of the Federal Food, Drug and Cosmetic Act	54

Figure 1.1 *Benchmarks in the regulation of pediatric drug development.* Source*: Modified from [70,71].*

2000	• Children's Health Act	55
	• ICH E11 Guidance, Clinical Investigation of Medicinal Products in the Pediatric Population	56
2001	• Adaptation of HHS Subpart D (pediatric) regulations to FDA regulated research	57
2002	• Best Pharmaceuticals for Children Act (BPCA), Public Law 107–119	58
	• Pediatric Research Equity Act (PREA)	59
	• Pediatric Rule was prohibited by a federal court, which ruled that Congress had not given the FDA authority to require extensive Testing of drugs for children	60, 61
2004	• NTP Center for the Evaluation of Risks to Human Reproduction Publishes Fluoxetine Report	62
2004	• FDA (CBER) Guidance for Industry and FDA Staff, Premarket Assessment of Pediatric Medical Devices	63
2005	• EMA Draft Guidance for Industry	64
2006	• FDA (CDER) Final Guidance for Industry, Nonclinical Safety Evaluation of Pediatric Drug Products	65
2007	• FDA amendments act (this reauthorized both the BPCA and the PREA until 2012)	66
	• WHO – "Make medicines child size" initiative	11
	• European Medicines Agency (EMA) Paediatric Regulation (Regulation (EC) No. 1901/2006)	67
2008	• Nonclinical working group established in EU	68
	• Committed for Human Medicinal Products (CHMP), Guideline on the need for non-clinical testing in juvenile animals of pharmaceuticals for paediatric indications	64
2009	• ICH M3(R2) briefly addresses juvenile toxicology studies	69

FUTURE

Figure 1.1 *(Continued)*

1.2 USE OF ANIMALS TO SUPPORT PEDIATRIC DRUG DEVELOPMENT

In 1977, the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research issued a report regarding research involving children [37]. In that report, the commission argued two points to support their position for conducting clinical trials in children. The first argument was that there were no suitable alternatives to the pediatric population and the second voiced the consequences of not conducting pediatric clinical trials, for example, perpetuation of risky

TABLE 1.3 Examples of Drugs that Exhibit Different Toxicities in Pediatric and Adult Populations

Drug	Observations	Ages Most Affected
Acetaminophen	Overdose results in death from liver toxicity; children possess a higher rate of glutathione turnover and more active sulfation	Adult
α-Interferon	Spastic diplegia	Infant
Aminoglycosides	In infants with *Clostridium botulinum*, the gastrointestinal tracts may have increased neuromuscular blockade and prolonged severity of the paralytic phase	Infant
	Vestibular balance and hearing deficiencies as well as renal disease	Adult
Aspirin	Results in alkalosis, acidosis, respiratory distress, and death	Child
β-Blockers	May cause hypoglycemia	Infant/Child
Chloramphenicol	Results in ''gray baby syndrome'' with vascular collapse and death; immature liver fails to conjugate free chloramphenicol to glucuronide, and the kidneys fail to excrete the free chloramphenicol	Infant
Influenza vaccine	Less effective in infants younger than 6 months	Infant
Methotrexate	Liver cirrhosis	Adult
Quinolone antibiotics	Tendon pathology noted as a complication of therapy	Adult

Source: Modified from Ref. 74.

practices, use of unsanctioned practices, and failure to develop new drug therapies for the pediatric population [37]. In addressing the lack of suitable alternatives to children, the commission noted that "possible alternative populations. . .are animals and adult humans, but there are limitations to both" [37] as noted in Table 1.4. While these limitations may have been most applicable to the time frame that these arguments were made in, history and experience provide the best scientific argument as to why juvenile animals can be useful to generate information to support pediatric drug development.

Although juvenile animal toxicity studies are required on a case-by-case basis to support pediatric clinical programs, testing in juvenile animals is not without questions. Two key outstanding questions are as follows:

1. How have these juvenile animal studies contributed to the overall safety assessment for a compound?
2. Have they identified pediatric-specific concerns that would have otherwise been missed in a standard young adult animal safety assessment?

TABLE 1.4 Limitations to the Use of Animal Models and Adults as Alternatives for Research in Children

1. No animal model is available for diseases that affect children or adults (e.g., cystic fibrosis and Down's syndrome)
2. Animal models are inappropriate for studying certain processes that are uniquely human (e.g., development of speech and cognitive functions)
3. The amount of brain development that occurs in humans after birth has no parallel in the animal world, and studies of such development must be done in humans
4. Normal biological measures or functions in animals (e.g., blood sugar levels or drug metabolism) are not consistent between different animal species and cannot be extrapolated to humans; thus, it eventually becomes necessary to examine the function in human subjects
5. No adult models exist for disorders that are unique to children (e.g., hyaline membrane disease, erythroblastosis fetalis, infantile autism)
6. Studies of normal development and of such phenomena as the ''critical period'' and child–parent interactions can be conducted only in children

Source: Modified from Ref. 37.

Additional questions would be the following:

1. How sensitive are juvenile animals to detect changes seen in humans?
2. Do the changes in juvenile animals translate to the intended pediatric population?

Conducting juvenile animal studies are not without risk as findings may not have clinical relevance and could impede or halt bringing important medicines to pediatric populations. Regardless of the questions and risks, clinical testing in pediatric populations is highly sensitive from an ethical and societal standpoint. Therefore, the most conservative approach is to test first in juvenile animals. Only in cases of prior pediatric experience can the importance of these studies be minimized. Some of the challenges that exist for both clinical and nonclinical pediatric testing are outlined in Table 1.5. Clearly, a forum is needed to gather the data for specific compounds and to assess the contributions of juvenile animal toxicity testing as it relates to pediatric drug development.

When should nonclinical studies in juvenile animals be considered? Before clinical or nonclinical studies are conducted to support pediatric drug development, there are several key points to take into consideration (Table 1.6). During the decision-making process, evaluation of the clinical studies that were conducted in human adults is required to determine the tolerability, bioavailability, pharmacokinetic properties, and toxicological potential of the medical product. Second, data generated during nonclinical studies in adult animals must be reviewed to evaluate

TABLE 1.5 Current Challenges in Pediatric Drug Development

Challenges	Pediatric Clinical Trials [8,72]	Nonclinical Pediatric Study [75]
Ethical	1. Clinicians who prescribe drugs off label with insufficient data pertaining to the pediatric population 2. Drug companies that pursue pediatric clinical trials late in drug development 3. Lack of transparency in clinical research 4. Reluctance to change 5. Safety concerns 6. Children usually lack the legal right or maturity (emotional or intellectual) to consent to research 7. Appropriateness of payments for involving children in clinical research	1. The three *R*'s (reduction, refinement, and replacement)
Economic	1. Reluctance of pharmaceutical companies to invest in pediatric drugs (i.e., smaller market, higher liability) 2. Lack of profitability 3. Number of patients required for enrollment	
Logistical	1. Deficient infrastructure for pediatric drug studies 2. Limited availability of baseline information on frequency of disease and treatment options 3. Rapid growth and development of pediatric patients	1. Timing relative to the drug development program 2. Justification for the study design 3. Selection of the appropriate species 4. Number of species to be evaluated 5. Availability of nonhuman primates, including the appropriate number, gender mix, and age 6. Limited laboratories available to conduct studies in nonhuman primates 7. Age at sexual maturity (rodents vs. nonhuman primates) 8. Dose selection (frank toxicity vs. identifiable toxicity) 9. End points to evaluate (case by case)

TABLE 1.5 (*Continued*)

Challenges	Pediatric Clinical Trials [8,72]	Nonclinical Pediatric Study [75]
Technical	1. Lack of accepted end points 2. Lack of validated pediatric assessment tools 3. Dosing issues (i.e., imprecise measuring instruments and taste and palatability issues 4. Need for alternative oral formulations	1. Age at initiation 2. Route of administration 3. Duration of treatment 4. Sample volumes
Other	1. Unsuitable drug formulations for use in children 2. Lack of quality control with the formulations 3. Timing of the Pediatric Investigation Plan (PIP) 4. Compliance of research with federal regulations	1. Effects of group size on statistical comparisons 2. Clinical relevance of findings 3. Studies outside of the proposed indication 4. Changes in the proposed age group 5. Consistency regarding scientific advice 6. Regulatory inconsistencies (i.e., lack of uniformity between the United States and the European Union)

the potential risk that a medicinal product may pose to the pediatric population. If these data are insufficient to support pediatric drug development in the intended pediatric age group, the current view of the regulatory agencies [64,69,73] is to proceed with appropriately designed nonclinical studies in juvenile animals. In addition, nonclinical studies in juvenile animals are particularly important when toxicity occurs in adult target organs that undergo significant postnatal development [73]. The "margin of exposure between animals and humans, as well as the magnitude of exposure difference between the adult and the pediatric population at clinically relevant doses" [64] must be taken into consideration when evaluating the need for nonclinical studies in juvenile animals.

Another point to consider is the ability to predict, from the existing nonclinical and clinical data, whether a drug will demonstrate different, the same, or no toxicities when administered to the intended pediatric patient. These predictions are age dependent [64]; therefore, it is reasonable to presume that the need for nonclinical studies in juvenile animals is indirectly proportional to the age (i.e., preterm babies $>$ adolescents; Fig. 1.2). The timing of the nonclinical studies in juvenile animals in relation to the pediatric clinical trial is dependent on the duration of exposure in pediatric subjects (i.e., long term or short term) and the availability of preexisting clinical data [69,73].

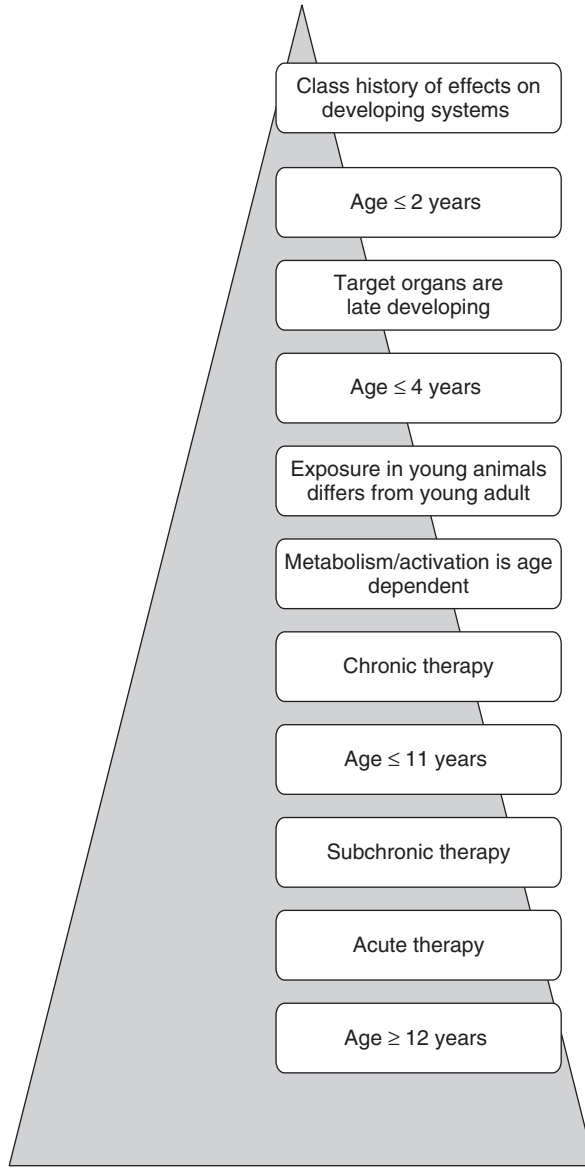

Figure 1.2 *The ability to predict from the existing nonclinical and clinical data as to whether studies in juvenile animals are necessary increases with age. Therefore, the likelihood of conducting a nonclinical study in older juvenile animals decreases. In addition, the duration of treatment and the type of therapy are also factors that determine whether a nonclinical study in juvenile animals is warranted.*

TABLE 1.6 Prestudy Considerations for Pediatric Programs

Consideration	Clinical [72]	Nonclinical [64]
Population	• The prevalence of the condition to be treated in the pediatric population • The age range of pediatric patients likely to be treated with the medicinal product • Whether there are unique pediatric indications for the medicinal product • The need for the development of pediatric-specific end points • Unique pediatric (developmental) safety concerns with the medicinal product, including any nonclinical safety issues	• Intended or likely use of a drug in children • Any established (or likely) temporal developmental differences (animal vs. human)
Disease state or condition	• The seriousness of the condition to be treated • The availability and suitability of alternative treatments for the condition in the pediatric population, including the efficacy and the adverse event profile (including any unique pediatric safety issues) of those treatments	• Identification and use of end points (i.e., biomarkers) relevant to identifying target organ toxicity across species and across ages
Formulation	• Potential need for pediatric formulation development • Whether the medicinal product is novel or one of a class of compounds with known properties	• Whether the route of administration is the same as the clinical route • Whether the vehicle is the same as the clinical vehicle • Whether the route and the vehicle are the same as in the adult animal studies • Whether the route and vehicle are appropriate for juvenile animals
Experimental design	• Duration of treatment	• Timing of dosing relative to phases of growth and development (pediatric populations vs. juvenile animals)
Existing data	• Extent of safety data in adults and/or the pediatric population in relevant age groups • Relevance of pharmacokinetic data	• When data from human safety and previous animal studies are insufficient for safety evaluation in the intended pediatric age group • Potential differences in pharmacologic and toxicologic profiles between mature and immature systems

As described below, the Food and Drug Administration (FDA) guidance [73] is clear on when nonclinical studies in juvenile animals are not necessary:

1. additional data would not alter the existing perspective regarding hazard assessment based on data generated from structurally similar products within a therapeutic class;
2. existing clinical data do not indicate any adverse event during clinical use;
3. target organ toxicity would be comparable between adults and the pediatric population (the organ in question is functionally mature in the intended pediatric age group); and/or
4. younger children with functionally immature organ systems are not expected to receive the medicinal product.

1.3 CURRENT REGULATORY PERSPECTIVES

Over the years, great strides have been made by various governmental agencies [6] and within the pharmaceutical and health care industries to rectify the disparity in the development and use of age-appropriate medicines to treat pediatric diseases and illnesses; however, challenges in pediatric drug development still exist. Some of the benchmarks in pediatric drug development are outlined in Fig. 1.1. Since the early 1990s, the focus on pediatric drug development has greatly increased. This is due, in large part, to increased regulatory efforts. Health authorities have driven progress in expanding the clinical database for pediatric use of therapeutics through a "carrot and stick" approach.

Starting first with the FDA [73] and more recently through the European Medicines Agency (EMA) [64], members of the pharmaceutical industry are required to address pediatric drug development early in their development programs ("stick") with the potential reward ("carrot") of six months additional exclusivity for the drug. The FDA and EMA differ in their timing to address pediatric development, with the EMA [64] requiring this after phase I through the submission of the pediatric investigational plan (PIP). In general, the FDA requires this to be addressed at the end of phase II. Owing to the importance of obtaining safety data in the adult population before proceeding into the pediatric population, the EMA approach seems fairly aggressive in terms of costs and risk. However, in practice, the pharmaceutical industry is gaining a better understanding of the PIP as a dynamic document that initially sets the commitment by the drug company for pediatric development. A deferral (e.g., in selected age groups) or a waiver can be obtained if pediatric use is deemed not to be appropriate. As a pharmaceutical company gains further information about a drug, the PIP is modified with a more detailed clinical and preclinical strategy. The FDA Written Request [54] submitted later in a compound's development is a document that usually has greater detail on the strategy for assessing development and use in pediatric populations. These differences between the agencies (and often among