PEDIATRIC NON-CLINICAL DRUG TESTING

PRINCIPLES, REQUIREMENTS, AND PRACTICES

EDITED BY
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Chapter 9: Juvenile Toxicity Study Design for the Rodent and Rabbit

Pediatric Nonclinical Drug Testing

Principles, Requirements, and Practices

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

Published simultaneously in Canada.

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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

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.

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.

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Chapter 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 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].

Table 1.1 Disease States Observed in Children

Source: Modified from Ref. 90

• 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

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.

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

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
2000	• Children's Health Act	55