PART I

PAST, PRESENT, AND FUTURE OF PEDIATRIC DRUG DEVELOPMENT

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CHAPTER 1

A New Model for Children

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Januscz Korczak (1878–1942), a noted author, founder of modern day orphanages in Poland, and posthumously honored as ''pediatrician'' by the American Academy of Pediatrics, has long been known as a children's advocate. Korczak spoke of a Declaration of Children's Rights long before any such document was drawn up by the Geneva Convention in 1924 or the United Nations General Assembly in 1959. Excerpts of his writing as a call to action include many famous aphorisms including: ''Love the child, not just your own'' and ''Who asks the child for his opinion and consent? As the years pass, the gap between adult demands and children's desires becomes progressively wider.''

The concept for this book grew out of my 20-year career as a pediatrician and pediatric specialist and became an even more urgent endeavor since I am now involved in drug development for children at Johnson & Johnson. The development of a book devoted to the critical issues involving children, of all age groups from preterm to adolescents, has been a personal mission since I have entered the pharmaceutical industry. From partnership and colleagueship, this book is a multidimensional text of all aspects and stages of the pediatric drug development process, coedited with academic and industry colleagues, John N. van den Anker and Steven A. Silber. Given the rapid evolution of regulatory policy governing drug development for children, it is a timely book that should be a valuable resource to industry, regulatory agencies, academia, and investigators worldwide.

Even in the so-called developed world, there are significant unmet medical needs for both adults and children. Moreover, the history of drug development is clearly one of neglecting the specific needs of children, by assuming, incorrectly of course, that data generated in

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adults can be applied directly to children. Thus, this new textbook addresses the significant and unmet needs of infants and children regarding proper drug development. For decades, the needs of infants, children, and adolescents have been ignored in the drug development process. For decades, Shirkey[1] has described infants and children as ''therapeutic orphans,'' attesting to the fact that drugs are not often developed for their specific and unmet medical needs. The awareness of the differences between the pediatric patient and the adult patient has in large part not been adequately addressed by the pharmaceutical industry. Drugs are used in children every day with little guidance on appropriate dosing based on a lack of understanding of the specific pathobiology, metabolic and physiological differences, and developmental changes that characterize the differences from the adult subject. Without understanding the differences between the child and the adult, there have been many examples of therapeutic misadventures, including thalidomide, elixir of sulfanilamide, and chloramphenicol. These three of many examples have led to the death of infants and children due to the lack of appreciation of the developmental differences of infants and children from the adult subject. The potential adverse impact on the pediatric patient without understanding the individuality of the pediatric subject is not acceptable. Far beyond the deaths, however, are the many potentially preventable adverse drug reactions or decreased efficacy in children, which occur because of over- or underdosing and unrecognized drug–drug interactions because the clinical information was never developed in pediatric populations.

The scope of this book addresses the unmet medical needs of all stakeholders to develop a new model of collaboration for the benefit of children who require therapeutic options supported by data generated in appropriate populations. This book addresses the scientific background of the differences between the pediatric and adult patient, the ethics of exploring these differences in clinical development programs, the business case for proper development of drugs for children, the technical feasibility, and the process that is necessary for a comprehensive pediatric drug development program. The applications of these approaches will benefit all stakeholders because it will result in better and safer drugs for the pediatric population.

The chapter flow represents the importance of this new model, integrating the needs of all stakeholders in the drug development process: government, academia, parents/patient organizations, and pharmaceutical industry. We start with a historical perspective of pediatric therapeutics, outline the population demographics, develop the business case for proper pediatric drug development, and review the ethics demanding a new model, and then we present the unique functional areas for which unique expertise is required. These functional areas represent the cornerstone of the pediatric drug development process: regulatory directives from Food and Drug Administration (FDA), the European Medicines Evaluation Agency (EMEA), and Japan (U.S., EU, and Japanese perspectives), preclinical/developmental toxicology, clinical pharmacology, clinical and operational development including safety, CMC/formulation development and case examples of successes.

Why have these issues been ignored for so long and what accounts for the changing environment? The economics of drug development together with a narrow interpretation of the ''ethics'' of drug development for children dictated that, despite rare occasions of specific agents developed for niche diseases, first indications for new chemical entities (NCEs) would be in adults. Approved drugs would then be ''downstreamed'' for children, without, in many cases, additional clinical trials or even pharmacokinetic (PK) studies. Change has come largely through the actions of governmental (FDA) incentives, including the Best Pharmaceuticals for Children Act and the Pediatric Research Equity Act. Due to a ''perfect storm'' of regulatory guidances, the interest of pediatric experts from academia, and

an evolving work force in industry who understood the business case for proper drug development for drugs for children, this book has been born.

It is with great honor and pride that this mission has now been completed. Targeting the needs of children is an important task for all societies, in both developed and ''developing'' countries, where the impact of utilizing proper therapies proven to be safe and effective has very significant medical and economic consequences.

Nelson Mandela stated that ''there can be no keener revelation of a society's soul than the way in which it treats its children.'' It is with pride that John, Steve, and I sincerely hope that this textbook brings luster to this issue and harnesses the critical and relevant topics in pediatric drug development.

Good reading!

REFERENCE

1. Shirkey H. Therapeutic orphans. *Pediatrics* 1968;72:119–120.