Iftekhar Mahmood
Gilbert Burckart
Editors

Fundamentals of Pediatric Drug Dosing

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Preface

The fundamentals of pediatric drug dosing are still evolving. While this may sound strange in the twenty-first century, it is a true statement. From 1950 to 1980, a sense of importance of understanding pediatric drug therapy came about, but the ability to apply scientific principles to pediatric drug dosing was impossible. While the science of pharmacokinetics and pharmacodynamics advanced from 1980 to 2000, few investigators attempted to apply these principles to pediatric dosing. From 2000 to the present, due to legislation in the USA and in Europe, we went from essentially zero to well over 1000 pediatric drug development trials that have been conducted and submitted to the US Food and Drug Administration.

So many pediatric trials in such a short period of time led to inevitable failures, in some cases failure was due to a poor understanding of drug dosing. But the encouraging development is that we are learning at a rapid pace, and the full attention of many more scientists is now trained on the pediatric patient. The pediatric patient, who ranges from an extreme premature infant weighing 1.0 kg to an adolescent weighing 70–120 kg, presents a remarkable challenge in understanding the science of drug dosing.

Therefore this book is very timely, and should provide both the student and the scholar with new information on a comprehensive list of topics required to properly understand pediatric drug dosing. With the regulatory changes that are described that will bring us drug development studies in newborns for the first time, new ground is continuing to be broken in the science of drug dosing and its application to pediatric patients. At the same time, I have to admit that we have a considerable amount to learn, and the next decade (or two!) will continue to bring us new models, new concepts, and perhaps best of all, better dosing of new drugs for the welfare of our pediatric patients.

Silver Spring, MD, USA — Gilbert J. Burckart

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Chapter 1
Pediatric Drug Development and the Regulatory Changes That Are Creating the Science of Pediatric Dosing

Gilbert J. Burckart

1.1 Introduction

The dosing of drugs in children has always been important but has not always been a science. When the great majority of drugs were not studied in pediatric patients during drug development, pediatricians still had to treat their patients in the best manner possible. That often meant trial and error, and treating a sick child with a guess related to the drug dose. As expected, using drugs "off label" often resulted in ineffective therapy or adverse effects. Published experience helped, but it came out slowly, and initial observations were frequently based on very few pediatric patients. The plight of pediatric patients requiring drug therapy needed a voice.

Into this environment came a pharmacist and pediatrician who became the voice of sick children. Dr. Harry Shirkey was originally trained as a pharmacist and worked at Cincinnati Children's Hospital, which inspired his interest in pediatric drug therapy. Shirkey later obtained his M.D., specialized in pediatrics, and was an advocate for better pediatric drug information throughout his career. In 1963, Dr. Harry Shirkey proclaimed that, "By an odd and unfortunate twist of fate, infants and children are becoming therapeutic or pharmaceutical orphans" [1]. Besides pointing out that children were being neglected in the drug development process, Dr. Shirkey made a major contribution through his *Pediatric Dosage Handbook* which was published in 1977 [2]. Initially, drug dosages for pediatric patients were almost completely on the basis of prior clinical experience and not on any scientific approach to dosing.

Two separate but mutually supportive directions of advancing pediatric drug development took place during the late 1960s until the 1990s. One direction was the development of the science of pediatric clinical pharmacology, and the other direction was the regulatory preparation that was necessary for the eventual legislative

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acts which enabled pediatric drug development over the past 15 years. The development of the science of pediatric clinical pharmacology was led by Dr. Sumner Yaffe.

Sumner Yaffe, M.D., was a Fulbright Scholar, and from the beginning, his dedication was to understanding the impact of drug therapy in newborn infants. He became the director of the Clinical Research Center for Premature Infants at Stanford and then moved to establish a Pediatric Clinical Pharmacology Unit at Buffalo Children's Hospital. While at Buffalo, Dr. Yaffe's research was significantly impacted by collaboration with scientific leaders in the developing field of pharmacokinetics. In particular, research collaborations with Drs. Gerhard Levy and William Jusko added the quantitative approach to pediatric clinical pharmacology that continued throughout Yaffe's research career and continues today in the application of modeling and simulation to pediatric drug dosing and trial design. This transition can be seen in the period covering the early 1970s in publications with Levy [3] and Jusko et al. [4, 5] and separately by Yaffe and Rane [6]. The translational aspect of this work to clinical pediatrics was an important part of Dr. Yaffe's approach to pediatric clinical pharmacology.

The regulatory preparation for advancing pediatric drug development occurred in the 1970s. In 1974, Congress passed the National Research Act and Title II of the Act established the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. Also in 1974, the American Academy of Pediatrics (AAP) published a report commissioned by FDA titled "*General Guidelines for the Evaluation of Drugs to be Approved for Use during Pregnancy and for Treatment of Infants and Children*." Based on this document, the FDA released the Guidance for Industry in September 1977 on the "General Considerations for the Clinical Evaluation of Drugs in Infants and Children." Also in 1977, a National Commission Report was published on "*Research Involving Children*." Then in 1979, the FDA promulgated a Regulation on *Pediatric Use* Subsection of Product Package Insert *Precautions* Section (21 CFR 201.57 (f)(9)) which established a place in drug labeling for pediatric precautions. All of this regulatory activity was an important precursor for the conduct of scientific investigations involving pediatric subjects, but little of this research involved drug development though the 1980s and 1990s.

With Dr. Yaffe as the director of the Center for Research for Mothers and Children at the National Institute of Child Health and Human Development, National Institutes of Health (NIH), the next major advance for pediatric clinical pharmacology was the establishment of the Pediatric Pharmacology Research Units (PPRUs) in 1994. Yaffe theorized that having a number of established and qualified research teams in pediatric clinical pharmacology in the USA would encourage the industry to use these sites as a way of gathering pediatric information to support drug labeling and lessen fears regarding the liability of conducting research in children. The PPRUs survived for three NIH funding cycles and served as a training ground for young pediatric clinical pharmacologists.

The PPRUs alone were not enough to stimulate drug development in pediatrics, but the pediatric regulatory professionals brought a new approach. In 1992, the Better Pharmaceuticals for Children Act was introduced in Congress by Senator

Nancy Kassebaum, which provided a financial incentive to manufacturers who conducted pediatric studies. This concept of providing a 6-month patent extension for conducting pediatric studies was included as part of the FDA Modernization Act of 1997 and was continued as the Best Pharmaceuticals for Children Act (BPCA) in 2002. The alternate regulatory approach of requiring the sponsor to conduct pediatric studies if the product was going to be used in pediatric patients was attempted through the Pediatric Rule of 1998, but this rule was enjoined in 2002 as an overextension of the FDA's authority. Subsequently, the Pediatric Research Equity Act (PREA) was introduced to Congress and was enacted in December of 2003 to ensure that pediatric studies would be conducted when the pediatric indication was the same as the adult indication.

The renewal of BPCA and PREA with the FDA Amendments Act of 2007 for another 5 years led to the discussion of the need for these acts to be permanent. On July 9, 2012, the FDA Safety and Innovation Act (FDASIA) of 2012 was signed by President Barack Obama with very little fanfare. The permanent enactment of BPCA and PREA with the FDA Safety and Innovation Act (FDASIA) of 2012 has now provided the stable foundation for the application of the science of pediatric clinical pharmacology started by Yaffe 50 years ago. That the pediatric section of FDASIA was the culmination of 50 years of work by pediatricians, and pediatric clinical pharmacologists went virtually unnoticed. However, 50 years of progress in pediatric clinical pharmacology by a relatively small group of people has provided much of the background for the science pediatric drug development today.

1.1.1 Problems in Designing Pediatric Drug Development Studies

Although the number of pediatric studies has increased remarkably with the enactment of BPCA and PREA, the science of predicting pediatric doses and designing pediatric trials is still developing. The science of designing clinical trials for pediatric patients has advanced considerably in the past decade.

1.1.1.1 Identification of the Appropriate Pediatric Dose

The identification of the correct pediatric dose remains the primary problem in pediatric clinical trials. Since there are very few situations in which a failed trial in pediatric patients can be repeated, getting the dose right prior to entering the efficacy and safety studies is critical. Some of the approaches to correcting this problem include modeling and simulation. The addition of studying a range of drug doses in pediatric patients, either in the PK/PD study or in the efficacy trial, ensuring that precise PK estimates are obtained in each age group, and performing an interim analysis have also been used to prevent conducting a failed pediatric trial.

1.1.1.2 Failed Trials

We have learned a great deal from the pediatric drug development trials that have failed, and they have been recently reviewed [7]. A prior reference suggested that as many as 42 % of BPCA trials failed to get labeled by the FDA for a pediatric indication. In the failed trials review, dosing problems were involved in the failures for 25 % of the pediatric studies. Two primary issues were identified: Issue 1 was that a range of doses were not tested and involved products such as albuterol, anastrazole, clopidogrel, docetaxel, and fulvestrant. Issue 2 was limiting the pediatric drug exposure to that which has been shown to be efficacious in adults for a clinically distinct disease, and involved alfuzosin, bendamustine, bicalutamide, clopidogrel, docetaxel, eszopiclone, and tamsulosin.

1.1.1.3 Matching Drug Exposure to Adult Exposure

While the concept of matching pediatric exposure to adult exposure provides a starting point by which to develop a pediatric dosing regimen, routinely using this approach as a standard has several potential problems:

- This approach may have actually discouraged the further development of knowledge about pediatric pharmacodynamic (PD) markers which could be critical for establishing accurate dosing guidelines for pediatric patients. There are classic examples of differences in sensitivity to drug effect between pediatric and adult patients, such as occurs with digoxin.
- By limiting the dose range for pediatric studies, matching adult exposures may have led to a number of failed pediatric trials for new drugs, and thereby has restricted the use of potentially valuable new drugs for pediatric patients.
- Since most drug trials in pediatric patients are conducted one single time without an opportunity for refinement, matching drug exposure in the absence of a PD marker can result in a lost opportunity for pediatric patients.

While matching drug exposure to that observed in adults remains as a first step in establishing a pediatric dose, the concept of studying a range of doses during the developmental PK/PD stage is the most reasonable approach to avoiding study failure due to using the wrong pediatric dose. The exception to this is when exposure matching is being used to establish the pediatric dose when efficacy is being fully extrapolated from adults or another pediatric age group, as discussed in the next section.

1.1.1.4 Extrapolation of Efficacy

The concept of extrapolation of efficacy from adult patients to pediatric patients is an important component of pediatric study design and the use of exposure matching. Extrapolation is a concept that can change as our understanding of the

pathophysiology of a disease state in pediatric patients' changes. Subsequently, our use of pediatric clinical pharmacology tools is at first dependent on our understanding of the disease state in pediatric patients and in specific age groups. While a disease state in adolescents may be the same as in adults, the disease in infants and young children has to be considered separately. The highest percentage of successful pediatric studies that achieve a labeled indication in pediatric patients has been observed when extrapolation of efficacy was used. A complete review of previous pediatric studies using exposure matching for full extrapolation of efficacy in pediatric patients has recently been published [8].

1.1.1.5 Dedicated PK Studies

The design of the PK study in pediatric patients requires considerable planning. Conceptual errors have been made by both rigidly conducting dedicated PK studies in all age groups of pediatric patients and in being overconfident that population PK can be definitive enough in a small pediatric patient population to provide adequate dosing information. The former concept is demonstrated by an examination of the need for dedicated PK studies in adolescent patients, and a recent review of adolescent PK studies demonstrated that 95 % of the dosing between adults and adolescents is similar [9].

1.1.1.6 Use of Modeling and Simulation

Modeling and simulation are powerful tools that are now being used in drug development and have specific applications for pediatric patients. A number of the failed pediatric trials under BPCA and PREA could potentially have been avoided with appropriate planning using the tools of modeling and simulation. Drug developers are now building teams of people who have training in modeling and simulation, but who often lack any pediatric clinical experience. As this area matures, clinicians and modelers will have to develop a common understanding of the problems that can and that cannot be addressed using these tools.

An additional challenge related to modeling and simulation is to create an algorithm for the proper assessment of a model that has been created for pediatric drug development. Since models can be influenced by matters of practical expediency for the drug developer, a proper assessment of the pediatric model requires that a large number of possibilities related to clinical disease state and drug response in the pediatric patient have to be considered. Such an evaluation algorithm has not been developed at the present time, which then leaves open the question as to whether modeling and simulation will in fact improve pediatric drug development currently. The use of clinical trial simulation, which incorporates both biostatistical and clinical pharmacology concepts for pediatric studies, may represent a reasonable approach to modeling and simulation to prevent pediatric study failure.

1.1.1.7 Pediatric Studies in Special Populations

At the present time, very few dedicated studies in special populations (renal and hepatic impairment, pharmacogenetic variants) are conducted in pediatric patients. However, the use of information generated in adult patients may not be appropriate for adjustments in dosing in the pediatric population.

This is especially true of the youngest pediatric patients, where the ontogeny of developing physiologic systems and drug dispositional systems plays a significant role in drug effect. This is especially true for pharmacogenomic (PGx) markers, where 29 % of the currently identified PGx markers in FDA labels are not suitable for translating the adult information to neonates or infants [10]. An adequate assessment of the drug therapy from both an efficacy and a safety perspective should be considered for pediatric patients with renal or hepatic impairment and may necessitate studies in the pediatric population if adult studies do not adequately provide dosing information in all age groups.

1.1.1.8 Pediatric Study Design Issues

For some of the pediatric drug development programs, some basic study design issues were flawed. Two examples are included in the next section and include inadequate study planning to provide the studies necessary for drug labeling and structuring the pediatric studies to account for the placebo effect. The sometimes exaggerated placebo effect observed in pediatric patients has been well recognized previously [11–13].

1.2 Examples of Lessons Learned from Pediatric Studies Conducted Under BPCA and PREA

A multitude of factors may contribute toward unsuccessful pediatric studies, and experience suggests that trial design and dosing issues are especially critical. Three relevant examples follow to illustrate common pitfalls in these areas.

1.2.1 Example: Dose Selection

Clopidogrel is a widely used oral antiplatelet agent indicated for adult patients with a history of acute coronary syndrome or recent myocardial infarction, stroke, or established peripheral arterial disease. In order to obtain needed information related to the use of clopidogrel in the pediatric population, FDA issued

a formal written request in 2001. Subsequently, in 2005, a group from the Hospital for Sick Children in Toronto reported their experience with clopidogrel for prevention of thrombosis in children with complex heart disease after cardiac catheterization [14]. The authors note that clopidogrel was well tolerated at doses ranging from 1 to 6 mg/kg/day in a small group of patients aged 6 months to 16 years and suggest a starting dose of 1 mg/kg/day for children. In 2007, the final revision of the FDA's written request was issued. Importantly, no dose was specified at this point. The sponsor then in 2008 published the results of the Platelet Inhibition in Children On Clopidogrel (PICOLO) study [15], based upon a narrow dose range, which suggested that a clopidogrel dose of 0.2 mg/kg/day in neonates and infants achieves a platelet inhibition level similar to adults administered a 75 mg/day dose. This dose was questioned, even in a letter to the same journal [16]. Regardless, the 0.2 mg/kg/day pediatric dose, which is approximately fivefold lower than the approved adult dose on a per-weight basis, was carried forward into a multicenter, randomized, controlled trial in 906 neonates and infants with cyanotic congenital heart disease palliated with a systemic-to-pulmonary artery shunt. The results of this trial demonstrated no significant difference between clopidogrel and placebo for either the primary efficacy endpoint (all-cause mortality or shunt-related morbidity) or bleeding. The similarity of the treatment groups for bleeding rates is inconsistent with placebo-controlled studies of the long-term use of clopidogrel in adults, which show that clopidogrel causes excess bleeding. These results are consistent with an inadequate clopidogrel systemic exposure in neonates and infants who received 0.2 mg/kg/day dosing. The clinical pharmacology review pointed out that the maximum plasma concentrations of SR26334, the major inactive carboxylic acid derivative metabolite of clopidogrel, averaged 0.03 mg/L in neonate patients in the study. This value represents approximately 1 % of the SR26334 C_{max} in healthy adult volunteers administered a 75 mg clopidogrel dose. Overall, despite exposing over 900 children to clopidogrel, the results of this study were inconclusive. The clopidogrel label notes that "it cannot be ruled out that a trial with a different design would demonstrate a clinical benefit in this patient population."

Several lessons can be drawn from the clopidogrel pediatric drug development program. First, when a high degree of uncertainty exists relating to dose selection, a range of doses should always be tested. At the higher end of the dose range, a dose should be used that achieves drug exposure at least as high as established with an efficacious response in adults. Testing more than one dose provides valuable information regarding the dose–response relationship, which is critical to selecting the optimal dose to maximize the benefit-risk ratio.

Next, in pivotal efficacy trials that expose large numbers of pediatric patients to an unproven therapeutic intervention, a planned interim analysis should be included. The interim analysis should be tailored toward the specifics of the drug under investigation and may include an initial assessment of the primary and secondary outcomes, toxicity, and relevant PK/PD relationships. Intervention may be necessary

should the results suggest a high probability that one or more of the doses in the trial is either unlikely to result in clinical benefit or associated with a disproportionate degree of toxicity.

Finally, some form of therapeutic drug monitoring should be used when available to ensure that the desired effect is being achieved and could include serum drug concentrations or, in this case, a point of care test for platelet inhibition.

1.2.2 Example: Dose Finding for a Pediatric Indication That Is Different from the Adult Indication

Alfuzosin is an alpha1-adrenergic receptor antagonist indicated for the treatment of benign prostatic hyperplasia in adults. In 2006, a written request was issued to the sponsor to conduct studies of alfuzosin in pediatric patients aged 2–16 years old with elevated detrusor leak point pressure due to a neurological condition. Although these two diseases differ, the development plan focused on matching adult dosing on a per-weight basis. The alfuzosin doses administered in the pediatric studies (0.1 mg/kg/day or 0.2 mg/kg/day) were consequently selected based upon the approved 10 mg dose of alfuzosin in adults, which corresponds to 0.14 mg/kg/day in a 70 kg patient.

A total of 172 pediatric patients participated in a randomized, double-blind, placebo-controlled, efficacy and safety trial. The drug failed on the primary study endpoint which was the proportion of patients with a leak point pressure (LPP) <40 cm H_2O at the end of 12 weeks as a comparable proportion of patients in both alfuzosin treatment groups and placebo group were responders. For secondary efficacy endpoints, which was the absolute and relative change in detrusor LPP from baseline, the 0.2 mg/kg alfuzosin treatment group was numerically better than the 0.1 mg/kg/day and placebo groups, although the difference did not reach statistical significance. Based on the PK analysis, the 0.1 mg/kg/day dose in pediatrics provided exposure ($AUC_{0–24}$ and C_{max}) slightly lower and the 0.2 mg/kg/day dose in pediatrics provided exposure slightly higher than that of the 10 mg daily dose in adults.

The results of this study suggest that alfuzosin is not effective for reducing detrusor leak point pressure in pediatric patients with elevated detrusor leak point pressure due to a neurological condition. However, by failing to fully explore the tolerated dose range, it cannot be ruled out that higher doses may provide therapeutic benefit for this pediatric use with an acceptable toxicity profile. The approved adult dose should not necessarily be assumed to represent the therapeutic range for a different pediatric indication. The dose–response and exposure-response relationships may differ between two different yet related disease states. Previous reports have shown that alfuzosin doses up to 80 mg/day are well tolerated in adult patients

with essential hypertension [17], and therefore it would not have been unreasonable to test higher doses in children. Identification of the maximum tolerated dose in children combined with a clinical development program that evaluates the entire tolerated dose range may be judicious when the targeted disease differs between the adult and pediatric populations.

1.2.3 Example: Trial Design Regarding C_{max}-Matching and Controlling for the Placebo Effect

Rizatriptan was approved in 1998 for the treatment of migraine headache with and without aura in adults. The adult doses were 5 and 10 mg. An initial trial in adolescent patients in 1999 using the 5 mg rizatriptan dosage resulted in a negative study. In 2006, investigators reported that a dosage of rizatriptan that was adjusted to give adolescents of >40 kg body weight a 10 mg dose was successful in treating migraine headaches [18]. In 2009, the FDA issued a written request for rizatriptan in pediatric migraine headaches. The study included an enrichment design that excluded placebo responders after the first dose prior to randomization. Also, the adjusted dosage of 10 mg rizatriptan for adolescents over 40 kg body weight was used in this study. In the PK study, the Cmax of rizatriptan was similar for the 5 mg dose in the patients under 40 kg, for the 10 mg dose in the adolescents greater than 40 kg, and for the adults given 10 mg. The primary endpoint of pain freedom at 2 h was significantly greater than placebo, and the product is labeled for use in migraine headaches for adolescents.

The placebo effect in the study of migraine headaches is well recognized [12, 19]. Having a study design that compensates for the placebo effect, such as was used in this development program in the 2009 studies, is necessary. Also, the dosage of the first studies in adolescents in 1999 with the 5 mg dose was not based upon adequate knowledge of the drug's clinical pharmacologic profile.

1.2.4 Example: Trial Design and Study Planning to Achieve a Labeled Pediatric Indication

Famciclovir is an orally administered prodrug of penciclovir, a nucleoside analog DNA polymerase inhibitor with antiviral activity against herpes simplex virus types 1 (HSV-1) and 2 (HSV-2) and varicella zoster virus (VZV). The FDA issued a pediatric written request to obtain PK and safety data in children <12 years of age with HSV or VZV infections. Although the pediatric drug development program

provided useful information about the disposition of famciclovir across varying age ranges, a formal efficacy evaluation was not included in the trial design. After completion of the studies, extrapolation of efficacy data from adults with herpes zoster to children with chickenpox was deemed inappropriate. Although chickenpox and herpes zoster are caused by the same virus, the diseases are different in pediatric and adult patients. Thus, the information gathered from this written request was not sufficient to label the drug for pediatric use, despite the enrollment of over 100 pediatric patients in clinical trials of famciclovir.

This example illustrates the need to identify information necessary to label the drug for pediatric use prior to initiating any studies in children. Careful consideration of the disease process relative to adults and the applicability of extrapolation early in the planning process are essential. If extrapolation is not feasible, the study design should include predefined efficacy outcomes to objectively assess the use of the drug or biologic in the pediatric population. The collection of safety and pharmacokinetic data alone for a disease that is unique to children will not allow approval of a pediatric indication and therefore not provide the pediatric community with the necessary information to use the drug properly in pediatric patients.

1.3 The Path Ahead Under FDASIA

The IOM report on BPCA and PREA was issued at the end of February 2012 [20]. The report made a number of observations that are critically important for pediatric clinical pharmacology. One of the observations was that some pediatric studies did not reach their full potential because of problems that we should learn from, and this is discussed below. Another observation was that some pediatric populations were understudied, and this is particularly pertinent for the neonates and premature infants. The IOM report also recommended timelier planning of pediatric studies, and this problem was hopefully remedied by the requirements related to FDASIA.

Early planning for pediatric studies is essential from a clinical pharmacology perspective. Developing appropriate models is time consuming, and a thorough understanding of the pediatric disease process and use of the drug is essential for producing a viable model of dosing and the expected response. PBPK models will improve over time and may be able to compensate for developing models early in a drug development program when only a small amount of pharmacologic information is available from the adult population. Similarly, clinical trial simulation is complex and always involves making a number of assumptions but should be performed if it can assist in incorporating some of the concepts in the chapter to make pediatric clinical trials more uniformly successful.

1.4 Summary

The work of 50 years of development in pediatric clinical pharmacology has now led us to a point where we have a large number of pediatric trials being conducted. We should learn from these trials and apply that knowledge to design better pediatric trials in the future. FDASIA has given us both the opportunity and the responsibility to plan these pediatric studies early during drug development and to initiate pediatric studies as soon as possible. From a clinical pharmacology perspective:

- Planning for dose finding, sample size identification, and trial design is critical.
- Planning on the part of the sponsor and the FDA review divisions is essential for determining requirements for pediatric labeling.
- Additional research on pediatric biomarkers of drug response is needed.
- New clinical pharmacology tools should help to optimize the use of pediatric study data and increase the success rate for labeled pediatric indications.

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Chapter 2
Pediatric Physiology

Iftekhar Mahmood

Children are not small adults because the differences between adults and children are not simply due to body weight but also due to physiological and biochemical differences. These differences lead to different rates of drug metabolism and/or renal clearance of drugs in different age groups of children as compared to adults.

Adult-children differences in the efficacy and safety of drugs can be explained in part by the differences in the pharmacokinetics (PK) of drugs. The factors that substantially influence the PK of drugs are physiological (tissue volumes and blood flow rates, renal and biliary excretion), physicochemical (tissue-blood partition coefficient), and biochemical (rates of xenobiotic metabolism). The age-dependent changes of the aforementioned factors can lead to adult-children differences in the PK as well as response (pharmacodynamics) to the drugs.

2.1 Classification of Age Groups

The FDA guidance on pediatrics and International Conference on Harmonization (ICH) define age groups within pediatric population as follows:

- Premature or preterm newborns = less than or equal to gestational age of 36 weeks
- Term newborn infants = birth to 1 month
- Infants = 1 month to 2 years
- Children = 2–11 years
- Adolescent = 12–16/18 years

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It should be noted that the abovementioned classification of age groups is arbitrary and does not necessarily coincide with the physiologic changes in the pediatric population. At least for the first decade of life, physiologic changes occur rapidly but these changes are not a linear process.

2.2 Body Weight

For drug dosing, adjustment for weight is generally done for neonates, infants, and children. It is widely believed that body weight increases with age (from birth to adult), but in some cases, this may not be true (some obese children may be heavier than other children in the same age group). Body weight increases rapidly in childhood and adolescence and then declines slowly in later years.

2.3 Body Surface Area

In health risk as well as in toxicological assessments, prediction of dose of chemicals for humans from laboratory animals is based on body surface area (BSA). Many drugs, especially anticancer drugs, are administered to adults and pediatrics based on BSA. Since it is not practical to measure BSA of every individual during drug therapy, over the years, several formulae have been developed to estimate the BSA in an individual. Some of these methods are described below. The most commonly used formula to estimate BSA is Dubois height-weight formula [1].

$$\mathrm{BSA}\left(\mathrm{m}^2\right)=0.007184\times\left(\mathrm{Weight\,in\,kg}\right)^{0.425}\times\left(\mathrm{Height\,in\,cm}\right)^{0.725} \tag{4.3}$$

The Dubois equation was generated based on a sample size of nine subjects [2] and is not the only equation for the prediction of surface area rather many investigators have developed their own equations to estimate the surface area.

Another equation to estimate BSA was developed by Haycock et al. [3]. These authors also used weight and height in their formula.

$$\mathrm{BSA}\left(\mathrm{m}^2\right)=0.024265\times\left(\mathrm{Weight\,in\,kg}\right)^{0.5378}\times\left(\mathrm{Height\,in\,cm}\right)^{0.3964} \tag{4.4}$$

Another method to estimate BSA has been mentioned by Sharkey et al. [4] without using height. Equation 4.3 gives the relationship between BSA (in cm^2) and weight (W) in grams.

$$\mathrm{BSA}=4.688\times W^{\left(0.8168-0.0154\times\log W\right)} \tag{4.5}$$

Estimation of BSA from Eqs. 4.3, 4.4, and 4.5 gives different BSA values. For example, calculated BSA from Eqs. 4.3, 4.4, and 4.5 using an adult body weight of

75 kg and a height of 160 cm give values of 1.78, 1.85, and 1.94 m^2, respectively. Thus, the estimated surface area will vary depending on the equation.

Therefore, methods used for the estimation of surface area will give different estimates and any dose calculation based on these estimated surface area may be inaccurate. Over the years, many review articles have been published which challenge the concept of body surface area for the dose selection [3, 5–7].

BSA is greater relative to weight in newborns, but weight increases more rapidly than BSA during childhood and adolescence. For example, as compared to adults, the ratio of BSA to body weight in a 3-month and a 3-year-old child is 2 and 1.5, respectively.

2.4 Organ Weights

Haddad et al. [8] obtained data (from birth to 18 years of age) for several organ weights from Altman and Dittmer and developed polynomial equations to predict organ weights across age. Organ size, tissue volumes, muscle mass, and organ blood flow can also be described allometrically (related to body weight). The coefficients and exponents of allometry (from neonates to adults) for some organs and blood flow rates are shown in the following Table 2.1.

The allometric scaling of brain provided an interesting observation. When data were scaled across all age groups (neonates to adults), the correlation coefficient (r^2) between body weight and brain weight was not very strong ($r^2 = 0.774$). The back-extrapolation of the data showed considerable deviation of the predicted values from the observed values. The root mean square error (RMSE) was 0.037. The percent prediction error ranged from 5 to 46 %. The inspection of the allometric plot (Fig. 2.1) indicated that a single exponent may not be suitable to describe the entire data. Therefore, data were divided into two groups (neonates to 2 years) and >2 years to adults. This method of analysis led to improved prediction of brain weights in younger children and adults. The RMSE was 0.012. The percent prediction error ranged from 1 to 13 %. The exponents of allometry indicated that the brain weight

Table 2.1 The coefficients and exponents of allometry for some organs and blood flow rates

Organs/blood flow	Coefficient	Exponent	R^2
Liver	0.048	0.847	0.990
Kidneys	0.10	0.807	0.980
Heart	0.0065	0.903	0.999
Lungs	0.019	0.959	0.991
Brain	0.31	0.398	0.774
Brain (neonates to 2 years)	0.115	0.899	0.997
Brain (>2 years-adults)	1.0	0.075	0.987
Kidney BF	0.012	1.121	0.983
Hepatic BF	0.088	0.706	0.990

Raw data from Björkman [9]
The organ and body weights are in kilograms
Blood flow (BF) is in liters/minute and body weight is in kilograms

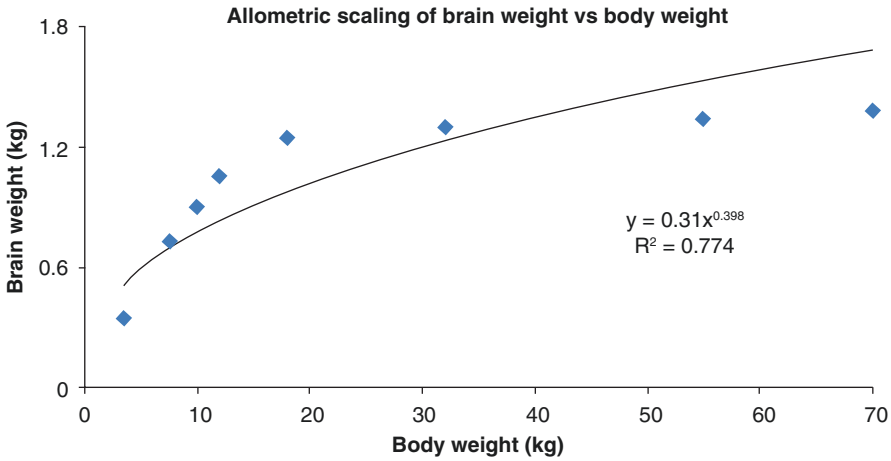

Fig. 2.1 Pediatric anatomy and physiology

increased rapidly from neonatal age to 2 years (from 0.35 to 1.12 kg), whereas the brain weight only slightly increased from 5 years onward to adults (1.29–1.45 kg). This is evident from the slope of allometry (0.075).

2.5 Pediatric Anatomy and Physiology

The following is a brief description of pediatric anatomy and physiology compared to adults (www.mstc.edu/instructor/randers/documents/pediatric).

2.5.1 Head

Proportionally larger size
Face small compared to head

2.5.2 Nervous System

Develops throughout childhood
Brain and spinal cord are less protected

Permeability of cell membranes is greater in infants; therefore, drug entry into some compartments is higher in the infants than adults. Brain-plasma ratios of some anticonvulsants are higher in infants and children as compared to adults.

2.5.3 Cardiovascular System

Maintains blood pressure better
Greater proportional circulating volume
Total blood volume is smaller but increases with age

2.5.4 Chest and Lungs

Ribs are less protective and chest muscles are immature
Lung tissues more fragile
Pulmonary contusions are more common
Airways are narrower at all levels
Trachea is softer and shorter
Metabolic oxygen requirements are double
Hypoxia develops rapidly

2.5.5 Abdomen

Immature abdominal muscles, less protective
Liver and spleen proportionally larger

2.5.6 Total Body Water

Volumes of intra- and extracellular water are higher in neonates, infants, and children. Total body water ranges from 78 % of the newborn's body weight to 60 % of the adult's body weight. Extracellular water represents about 45 % of the body weight in the newborn but only 20 % of the adult's body weight [10].

2.5.7 Enzymatic Activity

The enzymatic activity is less in infants and neonates than older children and adults. The activity of metabolic enzymes in neonates, infants, and children is about 20 %–70 % of adults; as a result, most of the drugs are eliminated slowly in neonates and infants than adults.

2.5.8 Renal Excretion

Although the ratio of kidney weight to total body weight in the newborn is twice than in the adult, the overall renal function is far less than the adults. Renal plasma flow and glomerular filtration rates, normalized based on body surface area in neonates, is only 30–40 % those of the adult [11]. Therefore, renal excretion of most of the drugs is much slower in the neonates than in the adults.

2.5.9 Skin Physiology

Fluhr et al. [12] compared skin physiology in children ($n = 44$; 1–6 years of age) with the skin physiology of adults ($n = 44$; average age 34.6 years) using a noninvasive bioengineering method. The adults were parents of the children. Only subjects with no skin disease (except atopic dermatitis) were included in the study. There were 31 females and 13 males in the adult group whereas there were 24 females and 20 males in the children group. The results of the study indicated that as compared to adults, the skin of the children had a significantly lower hygroscopicity, a lighter (higher L* values) and less red color (lower a* values), and an increased cutaneous blood perfusion.

2.6 Pediatric Obesity

Obesity is one of the health concerns round the globe especially, in the Western countries [13]. Obesity can be associated with disease states such as hypertension, diabetes, cardiovascular diseases, and osteoarthritis [13]. Obesity may also be associated with physiological changes such as increased cardiac output and blood volume [14].

Based on the literature review, Green and Duffull [13] concluded that in general, clearance does not increase proportionally with body weight in the obese and volume of distribution increases with excess adipose tissue. Allometric extrapolation from normal weight subjects to the obese indicated that both clearance and volume of distribution increases nonlinearly [15].

Body mass index or BMI is a simple and widely used method for estimating body fat [16]. BMI was developed by the Belgian statistician and anthropometrist Adolphe. It is calculated by dividing the subject's weight in kilograms by the square of his/her height in meters = (BMI = kg/m^2). The current definitions commonly in use establish the following values of BMI and associated weight [17]:

- A BMI less than 18.5 is underweight
- A BMI of 18.5–24.9 is normal weight
- A BMI of 25.0–29.9 is overweight

- A BMI of 30.0–39.9 is obese
- A BMI of 40.0 or higher is severely (or morbidly) obese

BMI as an indicator of a clinical condition is used in conjunction with other clinical assessments such as waist circumference. In a clinical setting, physicians take into account race, ethnicity, lean mass (muscularity), age, gender, and other factors which can affect the interpretation of BMI. BMI overestimates body fat in persons who are very muscular, and it can underestimate body fat in persons who have lost body mass (e.g., many elderly) [18]. Mild obesity as defined by BMI alone is not a cardiac risk factor and hence BMI cannot be used as a sole clinical and epidemiological predictor of cardiovascular health [19].

These days, obesity is not simply an adult issue, but children and adolescents are also becoming obese. As a result, pharmacokinetic data and dosing information in the obese children are also needed. However, PK data and dosing information in this age group are almost nonexistent.

2.7 Body Mass Index (BMI) and the Detection of the Degree of Obesity in Individual Obese Children and Adolescents

Widhalm et al. [20] studied to determine whether or not BMI is an appropriate index to measure the degree of obesity in individual obese children and adolescents. A total of 204 obese children and adolescents (105 boys and 99 girls; 6–17 years of age) were enrolled in this study. Total body electrical conductivity (TOBEC) was used for the measurement of fat. Body fat mass was estimated using the following equations:

$$\text{Children}\left(5-18\ \text{years}\right):\text{fat}=\text{weight}-\left(0.2772\times 0.5\left(E\times\text{height}\right)+1.232\right) \tag{4.27}$$

$$\text{Young adults}\left(19-40\ \text{years}\right):\text{fat}=\text{weight}-\left(0.2884\times 0.5\left(E\times\text{height}\right)-0.3951\right) \tag{4.28}$$

where E is TOBEC number.

Two TOBEC scans of the whole body were performed and averaged for each subject. Fat mass was calculated as

$$\text{Fat mass}\left(\text{kg}\right)=\text{body weight}\left(\text{kg}\right)-\text{fat}-\text{free mass}\left(\text{kg}\right) \tag{4.29}$$

Percentage body fat (PBF) was calculated as

$$\text{PBF}=\left(\text{fat mass}/\text{body weight}\right)\times 100 \tag{4.30}$$

A multiple regression analysis was performed with percentage body fat (PBF) as dependent variable and BMI, age, and gender as independent variables. BMI and PBF were correlated (overall: $r^2 = 0.65$; boys $r^2 = 0.63$ and girls: $r^2 = 0.68$). In boys younger than 10 years, 73 %, and in girls younger than 10 years, 63 % of the variance of PBF was explained by the BMI. In subjects 10 years or older, the correlation was poor (boys: $r^2 = 0.27$; girls: $r^2 = 0.37$). The authors concluded that BMI might be a useful parameter for epidemiological studies. However, in the individual pediatric patients, who are 10 years or older, it gives only a limited insight to the degree of obesity.

2.8 Pharmacokinetics in Obese Children

Changes in the body composition in obese patients may lead to changes in drug distribution. The smaller ratio of body water and muscle mass to total body weight as well as higher amount of body fat in the obese may lead to changes in drug distribution into various body compartments [13].

As mentioned earlier, there are very few PK studies in obese children. In a review article, Kendrick et al. [21] reported that there were limited pharmacokinetic and dosing information available in obese children mainly due to the lack of participation of obese children in the clinical trials. Koshida et al. [22] compared the PK of tobramycin and cefazolin between normal-weight and obese children. The study found that the absolute clearance (in mL/min) and volume of distribution at steady state were almost twice in the obese than the normal-weight children. The half-life was similar for both drugs in both groups of children.

In a population pharmacokinetic study of propofol in morbidly obese and nonobese adults, adolescents, and children, Diepstraten et al. [23] noted that the clearance of propofol increased allometrically with total body weight while there were two distinct slopes for age. The two slopes for age indicated an initial increase and subsequent decrease as a function of age.

Harskamp-van Ginkel et al. [24] performed a literature review related to the effect of obesity on drug disposition in children. Pharmacokinetic data were available for 21 drugs and the age ranged from newborn neonates to 29 years. Clinically significant pharmacokinetic alterations were observed in obese children for 65 % (11 of 17) of the studied drugs. Pharmacokinetic alterations resulted in substantial differences in exposure between obese and nonobese children for 38 % (5 of 13) of the drugs. Children received either a fixed dose (6 children), or based on body weight (10 children), or based on body surface area (4 children). The authors found no association between drug lipophilicity or Biopharmaceutical Drug Disposition Classification System and changes in volume of distribution or clearance due to obesity. The authors emphasized on conducting PK studies in obese children and adjustment of dose in obese children based on pharmacokinetic information.

Like PK, dosing information is also lacking in obese children. Lewis et al. [25] reported increased dose requirement of enoxaparin in obese children with venous thromboembolism (VTE) prophylaxis.

Moffet et al. [26] found that vancomycin trough concentrations were not different between obese and nonobese children. Based on their study, the authors recommended that the obese children should receive vancomycin based on actual body weight. In another study, Heble et al. [27] found that in obese pediatric patients, vancomycin initial trough concentrations were elevated based on total body weight dosing and recommended special attention to therapeutic drug monitoring in both obese and normal-weight children.

In short, at the moment, there is very little PK and dosing information in obese children, and in the absence of this information, it is difficult to conclude if dose adjustment is needed in the obese children as compared to normal weight children. Dosing in obese children as a function of linear body weight should be avoided since dosing requirement in obese children as compared to normal weight children may not be a linear function. The dosing consideration should also be based on the PK differences between obese and normal weight children rather than just simply body weight based. If the PK parameters such as clearance and volume of distribution do not differ between obese and normal weight children, then dose adjustment may not be required in the obese children. At the moment, it is also not known if extrapolation of PK parameters and/or dose from adults to the obese children can be accurately performed.

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Chapter 3
Developmental Pharmacology: Impact on Pharmacokinetics and Pharmacodynamics of Drugs

Iftekhar Mahmood

3.1 Introduction

Children are not small adults because the differences between adults and children are not only due to body weight but also due to physiological and biochemical differences. The differences in body composition and in the functions of the liver and the kidneys between children and adults are considered to be the main sources of pharmacokinetic differences between these two groups. In the neonates and infants, the physiological events change very rapidly as compared to body weight or size [1]. At least for the first decade of life, physiologic changes occur rapidly, but these changes are not a linear process [1–3]. The adjustment of dosing in pediatric population based on body weight or body surface area without considering the aspects of ontogeny is inappropriate because body weight or body surface area does not represent the true nature of overall organ function in the pediatric population. Therefore, dosing of drugs in children requires a thorough knowledge of ontogeny. Age-dependent pharmacokinetic and pharmacodynamic (where possible) studies can be helpful to find a safe and efficacious dose of a drug in children [1–3].

The important differences between adults and pediatric population in drug absorption, distribution, metabolism, and elimination are discussed below.

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3.2 Absorption

Absorption of drugs through gastrointestinal (GI) tract is influenced by many factors such as chemical form, particle size, solubility, chirality, etc. [4]. The rate of absorption of a drug by GI tract is dependent on the lipophilicity and the ionized form [4]. The more lipophilic a compound, the faster is its absorption. Similarly, the nonionized form of an acid or basic drug will be absorbed but not the ionized form. Most acidic and neutral drugs are absorbed from the stomach, but the basic drugs do not because they are largely ionized at low pH [4].

Due to the developmental changes in absorptive surface area of GI tract, the oral bioavailability of a drug can be substantially influenced [4]. Generally, the drugs are absorbed in neonates and infants much slower than the older children and adults; hence, the time to reach maximum plasma concentrations is longer in the very young [4]. Gastric acid pH is neutral at birth and gastric acid secretion reaches to the adult values by the age of 3 months [5]. Gastric emptying and intestinal motility are irregular in the newborn. Due to decreased capacity of intestinal bacterial flora as compared to older children and adults, the bioavailability of drugs in infants may increase [6]. Stomach acidity is decreased in the newborn and infants due to frequent intake of milk. When the pH of the stomach is high, drugs that are weak acids are absorbed more slowly than the drugs that are weak bases [7].

At birth, pancreatic and biliary functions are immature [8]. Pancreatic enzymatic activity, bile formation, bile acid synthesis, bile acid pool size, and bile acid intestinal absorption are at much lower levels at birth than the older children and adults. Pancreatic and biliary functions, however, rapidly develop with age. The net result of bile salt deficiency and pancreatic enzymes is that the bioavailability of drugs which require solubilization or intraluminal hydrolysis is reduced [9].

Intestinal enzymatic activity is age dependent. In a study, Johnson et al. [10] investigated the effects of age and coeliac disease on the activity of intestinal CYP3A4 in a pediatric population ($n = 104$; 2 weeks to 17 years of age). There were also 11 fetuses in the study. In normal pediatric patients (without coeliac disease), CYP3A4 activity increased with age (almost threefold increase in CYP3A4 activity between neonates and children >12 years of age). CYP3A4 was absent in fetal duodenum. In coeliac disease, the CYP3A4 activity was reduced than the normal children. Based on the results of the study, the authors concluded that the oral bioavailability of CYP3A4 substrates may be different in neonates than older children and adults. Coeliac disease may also affect the oral bioavailability of CYP3A4 substrates.

Stahlberg et al. [11] found that epoxide hydrolase and glutathione peroxidase activities are not age dependent, but the intestinal activity of cytochrome P-450 1A1 (CYP1A1) appears to increase with age. Glutathione-S-transferase activity decreases from infancy through early adolescence [12]. The activity of β-glucuronidase in the small intestine of infants is much higher (as much as

sevenfold) than the adults [13]. This may lead to enhanced bioavailability in infants for those drugs which undergo enterohepatic recirculation (chloramphenicol, indomethacin) [9].

Although, the most convenient route of administration of a drug is oral route, many drugs are given by subcutaneous or by intramuscular route. Percutaneous absorption may increase in neonates and infants due to thinner stratum corneum and increased cutaneous perfusion and hydration of the epidermis as compared to adults [14–16]. Due to higher ratio of total body-surface area to body mass in infants and young children than adults, the relative systemic exposure of topically applied drugs as well as drugs given by subcutaneous route in infants and children may be higher than in adults [17, 18]. Due to reduced skeletal-muscle blood flow in neonates and infants,, the rate of intramuscular absorption of drugs may also reduce [19]. However, there are also evidence of increased intramuscular absorption of some drugs in neonates and infants than in older children [20, 21].

3.3 Distribution

Drug moves to and from the blood and various tissues of the body. Water-soluble drugs stay in the interstitial space and blood for a longer period than fat-soluble drugs, whereas fat-soluble drugs tend to concentrate in fatty tissues. Drugs penetrate different tissues at different rates, depending on the drug's ability to cross membranes. For example, a highly fat-soluble drug such as thiopental enters the brain rapidly, but a water-soluble drug such as penicillin does not. Generally, fat-soluble drugs cross cell membranes faster than water-soluble drugs. For some drugs, transport mechanisms are the source of movement in or out of the tissues. Drug distribution may depend on body weight and age.

3.3.1 Body Composition

Body composition is age dependent (at least from newborn to childhood); therefore, physiologic space for drug distribution will vary until a certain age. Many factors such as physicochemical properties of drugs, blood flow, volume of extracellular water and adipose tissue, and protein and tissue binding affect drug distribution in the body [22].

The ratio of total body water to body weight is higher in newborns than in older children and adults (total body water decreases from 80 % of body weight at birth to 60 % at 1 year). Total body water gradually decreases with age and reaches to adult value by the age of 12 [23].

Volumes of intracellular and extracellular water are also higher in neonates, infants, and children as compared to adults. Thus, water-soluble drugs will have higher volume of distribution in newborns and infants on per kilogram body weight basis than adults. Similarly, infants have higher proportion of body fat than adults, which may result in larger volume of distribution for lipid-soluble drugs in neonates and infants than adults [1, 24].

3.3.2 Protein Binding

Plasma protein binding affects drug distribution and elimination. Drug–protein binding may be a reversible or an irreversible process. Drug–protein binding is influenced by a number of factors such as physicochemical properties of drug, concentrations of drug as well as concentrations of protein present in the body, the affinity between drug and protein, and disease states such as hepatic or renal impairment [24].

Human serum albumin (HSA) is most abundant protein in plasma. In healthy subjects, HSA concentration in plasma is about 40 g/L [24]. Lower levels of HSA can be found in pregnancy and disease states (renal and/or hepatic impairment) [24]. α1-acid glycoprotein is an important binding protein for basic drugs. α1-acid glycoprotein is a low molecular weight (40,000 Daltons) protein and the average concentration in plasma is about 400–1000 mg/L [25]. Its concentration in plasma rises in inflammation, malignant disease, and stress, whereas renal and hepatic diseases lead to its decrease in plasma [24].

Albumin and $_1$-acid glycoprotein concentrations are lower in neonates and infants than older children, thus increasing the free fraction of the drug (especially for highly protein bound drugs) in this population [22, 26]. Increase in free fraction of a drug may also increase drug distribution in the tissues and can produce adverse effects.

At birth, HSA concentrations are closer to adults (75–80 %), but α1-acid glycoprotein concentration is half of the adult concentrations [27]. The concentration of HSA in cord blood is 36 g/L as compared to 45 g/L in adult plasma [27]. α1-acid glycoprotein concentration in cord blood is 0.24 g/L as compared to 0.6 g/L in adult plasma [27].

3.3.3 Prediction of Protein Binding in Infants

Determination of protein binding in plasma in young children may be difficult due to the need of blood sample(s). McNamara and Alcorn [27] proposed a method for the prediction of unbound fraction of protein (f_u) in neonates and infants. The method utilizes adult unbound protein fraction and the ratio of infant and adult albumin concentrations. The following equation was used by McNamara and Alcorn to predict the f_u in infants.

$$f_{\text{u infant}} = \frac{1}{1 + \frac{P_{\text{infant}}}{P_{\text{adult}}} \times \frac{\left(1 - f_{\text{u adult}}\right)}{f_{\text{u adult}}}} \tag{5.1}$$

where P = molar protein concentration.

This simple approach provides an indirect method to estimate unbound fraction of protein in neonates and infants in the absence of direct measurement of protein binding.

3.3.4 Erythrocytes and Tissue Binding

Drug uptake by erythrocytes is a function of plasma protein binding [24]. Drugs that bind to erythrocytes may exhibit concentration-dependent uptake from plasma. Generally, drug binding to erythrocytes is a reversible process [24].

Tissue binding plays an important role in drug distribution [24]. Tissue binding has no influence on drug clearance but may affect the half-life of drugs. It is not known if tissue binding is related to pharmacological effect of drugs [24]. The relationship between apparent volume of distribution, drug binding, and plasma volume can be described by the following equation:

$$V = V_{\text{p}} + V_{\text{t}} \left(\frac{f_{\text{up}}}{f_{\text{ut}}} \right) \tag{5.2}$$

where V_{p} is plasma volume, V_{t} is tissue volume, and f_{up} and f_{ut} are the fraction of unbound drug in plasma and tissues, respectively.

Gorodischer et al. [28] studied the distribution of digoxin in the myocardium, skeletal muscle, erythrocytes, and plasma or serum in 19 infants. There was a linear relationship between myocardium and serum concentrations and no saturation was observed over the serum concentration range of 0.5–8.6 ng/mL. At any given serum concentration, myocardium uptake of digoxin was almost twice in infants as seen with adults. Erythrocyte:plasma concentration ratio of digoxin was three times higher in infants than the adults. In another study, Kearin et al. [29] compared digoxin binding with erythrocytes between neonates and adults. The results of the study indicated that the neonatal erythrocytes had 2.5 times as many digoxin-binding sites as adult erythrocytes. The authors suggested that the differences in binding properties resulted in the decreased sensitivity of digoxin in neonates and infants.

3.3.5 Blood–Brain Barrier and Membrane Permeability

Membrane permeability in the neonates is much higher than the older children and adults. The blood–brain barrier is immature in newborns and neonates and more permeable to drugs, which may lead to higher drug concentrations in the central nervous system of very young children [30, 31]. For example, first-generation H-1 receptors are lipophilic and can rapidly cross the blood–brain barrier in newborns and neonates than older children and adults [30, 31].

3.4 Metabolism

The major site of drug metabolism is the liver, but drug metabolism can also occur in the gastrointestinal tract, kidneys, lungs, and placenta. The hepatic drug metabolism can be divided into phase I and phase II reactions. Phase I reactions are mediated by CYP enzymes, whereas phase II reactions are involved with conjugation pathways (glucuronidation, sulfation, and glutathione). Enzyme systems in the liver of children mature at different rates and may be absent at birth or present in considerably reduced amounts [32]. The rates of drug metabolism in newborns and infants are much slower than in adults because the activity of metabolic enzymes in neonates, infants, and children is about 20–70 % of adults [32].

In the adult liver, the metabolic pathways are well defined but much less information is available for neonates, infants, and children. Due to developmental changes in drug metabolism, it is important to consider age-dependent dosing regimens in pediatrics. Enzyme-specific developmental changes in the metabolism of drugs are well known for many phase I and phase II drug-metabolizing enzymes. These developmental changes are described below.

3.4.1 Phase I Drug Metabolizing Enzymes

There is a substantial difference in mRNA, protein, and enzyme activity in infants and children as compared to adults. These differences produce different metabolic profiles and metabolic clearances between infants and adults. A summary of some important cytochrome P450 enzymes and their properties is presented below.

3.4.1.1 CYP3A

Quantitatively CYP3A is the most abundant CYP subfamily enzymes in the adult liver. The CYP3A subfamily consists of at least three isozymes: CYP3A4, 3A5, and 3A7. CYP3A4 is major adult liver enzyme but is present only in low levels in the

fetal liver. CYP3A4 activity gradually increases throughout infancy, exceeding that of adults, then declines to adult levels by the end of puberty [33, 34]. CYP3A4 is also found in the gut and gut 3A4 possibly matures by about 4 months of age [25].

In the infant population, CYP3A5 appears within the first week of life and remains constant up to a year of life. CYP3A7 activity is substantial in fetal liver and reaches to its maximum value by 1 week postpartum [35]. After that, CYP3A7 activity declines during the first year of life [36], and by the adulthood, CYP3A7 activity is almost 10 % that of fetal liver.

3.4.1.2 CYP1A2

CYP1A2 has negligible activity at the early stages of life [37, 38]. CYP1A2 could only be detected by age 1–3 months and reaches to adult level by 1 year of age [38]. The newborns and infants cannot metabolize caffeine to paraxanthine, a CYP1A2 pathway, suggesting that CYP1A2 is absent at the very early stage of life [37, 38].

3.4.1.3 CYP2C9 and CYP2C19

The CYP2C subfamily is about 20 % of the cytochrome P450 in adult liver. CYP2C9 is not detectable in fetal liver, but CYP2C9 activity develops rapidly in infancy, exceeds that of adults in children up to 10 years of age, and then declines to reach adult levels during puberty [39, 40]. By the age of 1 year, CYP2C9 activity is 30 % of adult value [41].

The poor metabolizer phenotype for CYP2C19 is due to a nonfunctional enzyme that is present in approximately 3 %–5 % of Caucasians and African Americans and in approximately 15–20 % of the Asian population [42].

Koukouritaki et al. [43] studied the developmental progress of liver microsomal CYP2C9 and CYP2C19. Two hundred thirty-seven subjects, age ranging from 8 weeks gestation to 18 years were included in the study. CYP2C9 catalytic activity was 1–2 % of adult values during the first trimester but gradually increased during the second and third trimesters to levels approximately 30 % of adult values. From birth to 5 months, CYP2C9-specific activity was higher by 4–5 times than those observed during the late fetal period. In children older than 5 months of age, CYP2C9 activity was similar to adults.

CYP2C19 protein and catalytic activities of 12–15 % of adult values were noted as early as 8 weeks of gestation and were similar throughout the prenatal period. CYP2C19 activity increased linearly over the first 5 months of life. In children older than 10 years of age, CYP2C19 activity was similar to adults [43].

3.4.1.4 CYP2D6

CYP2D6 consists of only 2 % of total CYP content of the adult liver, but its activity is of immense importance since it exhibits genetic polymorphism [44]. CYP2D6 activity leads to poor and extensive metabolizer phenotypes. Approximately 10 % of

Caucasian population is poor metabolizer [45]. CYP2D6 activity is negligible in fetal liver but is present in newborns as early as 7 days of life. CYP2D6 developmental activity may be complete by 1 year of age [36, 45].

3.4.2 Phase II Drug Metabolizing Enzymes

In phase II drug metabolism, compounds are conjugated with charged species such as glutathione, sulfate, or glucuronic acid [46]. Products of conjugation reactions have increased molecular weight and tend to be less active than phase I metabolism which often produce active metabolites [46]. Less information is available on the impact of ontogeny on the phase II enzymes than phase I enzymes, but it seems that the activities of phase II enzymes are also age dependent [47]. Some important conjugation reactions are summarized below.

3.4.2.1 Glucuronide Conjugation

Uridine 5-diphosphate (UDP)-glucuronosyl transferase (UGT) catalyzes the conjugation of glucuronide acid to their substrates. More than 18 different enzymes, divided into two families, UGT1A and UGT2B, have been identified in humans [48]. The ontogeny of UGT enzymes is not well known. The fetal liver has low levels of UGT1A1 protein and activity as compared to the adults, but UGT1A1 activity increases rapidly and reaches to the adult levels by the age of 3–6 months [49]. The UGT2B17 enzyme which metabolizes androgenic steroids is only 3 and 13 % of adult levels in fetal and intact liver microsomes, respectively [50].

3.4.2.2 Glutathione Conjugation

Glutathione-S-transferase (GST) belongs to a family of proteins responsible for the conjugation of glutathione with a wide variety of electrophilic or reactive lipophilic and alkylating agents. GST plays an important role in the metabolism of acetaminophen and naloxone in infants and children. Fetal activity of GST is detectable as early as weeks of gestation. The enzymatic activity varies from 66 to >100 % that of adults at birth [51, 52].

3.4.2.3 Sulfate Conjugation

Sulfotransferases belong to family of cytosolic proteins that catalyze the conjugation of inorganic sulfate. Based on a study, Levy et al. [53] concluded that acetaminophen undergoes glucuronidation in adults, but in newborns and young children, both sulfate and glucuronide conjugation occurs. Thus, in newborns and

young children, sulfate conjugation compensates for glucuronide deficiency for acetaminophen metabolism. Sulfate conjugation for morphine occurs in neonates before the development of glucuronidation [54].

3.4.2.4 Acetylation

N-acetyltransferase (NAT) is widely distributed in the tissues and NAT is responsible for the acetylation of number of drugs. There is very little information about the impact of ontogeny on acetylation. From the limited data, it appears that NAT activity develops as early as the first trimester and fetal liver can acetylate several substrates [44, 55], but overall activities of NAT are substantially lower in the fetal liver than that of adults. Infants less than 1 year of age are generally (83 %) slow acetylators [56, 57], but those infants who are fast acetylators reach to maturation by 2–4 years of age depending on the substrates [56, 57].

3.4.2.5 Aldehyde Oxidase

Aldehyde oxidase (closely related to xanthine oxidase) is a cytosolic enzyme, responsible for detoxification of several classes of drugs such as antimalarial, anticancer, antiviral, and antiepilepsy [58]. Tayama et al. [58] investigated the developmental changes of aldehyde oxidase activity in 101 Japanese children. The ages of the children ranged from 3 months to 12 years. Based on their study, the authors suggested that the dose of the drugs which are metabolized by aldehyde oxidase should be adjusted in children 1 year or younger. In the absence of dose adjustment, serious side effects such as liver or renal failure and nephropathy may occur to the pediatric population 1 year or younger.

3.4.2.6 Monoamine Oxidases

Monoamine oxidases (MAOs) A and B are flavin-containing enzymes and are involved in the metabolism of endogenous as well as exogenous amines. Kornhuber et al. [59] found that MAO-A activity was very high at birth but decreased rapidly during the first 2 years of life and remained constant thereafter. MAO-B activity was low at birth, remained unchanged during early childhood, and increased with age. Placenta contains both forms of monoamine oxidases but MAO-A is predominant [60].

3.4.2.7 Bile Acids

Bile acids are produced in the liver by the oxidation of cholesterol, conjugated (with either the amino acid taurine or glycine, or a sulfate, or a glucuronide) and are stored in the gallbladder. Bile acids are responsible for elimination of cholesterol from the

body, serve to emulsify lipids and fat-soluble vitamins in the intestine, and possibly help in reducing the bacteria flora found in the small intestine and biliary tract. Kimura et al. [61] analyzed 28 urinary bile acid concentrations in different age groups and found that bile acid synthesis and metabolism in the liver of developing infants are significantly different than the adults.

3.5 Renal Elimination

Besides hepatic metabolism, drugs are also eliminated by renal route. Renal excretion is a major route of elimination for many drugs. Drugs that are nonvolatile, water soluble, and have low molecular weight are generally eliminated by the kidneys. Renal clearance (CL_r) is defined as the volume of plasma that is cleared of drug per unit time through the kidneys [62]. There are several methods for the estimation of renal clearance, but the most commonly used method is as follows [62]:

$$CL_r = \frac{DU_{(0-\infty)}}{AUC_{(0-\infty)}} \tag{5.3}$$

where $DU_{(0-\infty)}$ is the total amount of drug excreted unchanged in the urine.

$AUC_{(0-\infty)}$ is the total area under the plasma concentration versus time.

Renal clearance can also be calculated by the following equation:

$$CL = \text{Total}\,CL \times f_e \tag{5.4}$$

where f_e is the fraction of the dose excreted unchanged in the urine.

Renal clearance is the sum of three processes:

- Glomerular filtration
- Tubular secretion
- Active or passive tubular reabsorption

In man, glomerular filtration rate (GFR) is approximately 125 mL/min. Renal clearance greater than 125 mL/min indicates that the secretion mechanism is involved, whereas renal clearance less than 125 mL/min indicates tubular reabsorption [62]. It is always possible that filtration, secretion, and reabsorption processes are simultaneously taking place during renal clearance of a drug.

3.5.1 Glomerular Filtration

At birth, kidneys are anatomically and functionally immature and the renal function in the newborns is limited. The glomerular filtration rate (GFR) is approximately 2–4 mL per minute per 1.73 m^2 in term neonates, but it may be as low as 0.6–0.8 mL per minute per 1.73 m^2 in preterm neonates [23]. In general, the GFR in neonates is

30–40 % of adult value [7]. By the end of the third week, GFR is about 50–60 % of the adult value [7]. The GFR increases rapidly during the first 2 weeks of life because of a postnatal drop in renal vascular resistance and increase in renal blood flow. GFR then rises steadily until adult values are reached by 1 year of age.

3.5.2 Tubular Secretion

Tubular secretion is an active transport process and is independent of plasma protein binding but dependent on renal blood flow [62]. Drug secretion also depends on the affinity of the drug for carrier proteins in the proximal tubule, the rate of transport across the tubular membrane, and the rate of delivery of the drug to the site of secretion [62]. All these factors can be mathematically described by the following equation:

$$CL_r = \frac{RBF \times f_b \times CL_i}{RBF + f_b \times CL_i} \tag{5.5}$$

where

RBF = renal blood flow
f_b = free fraction of drug in blood
CL_i = intrinsic secretion clearance

Tubular secretion is immature at birth and approaches adult values by 7 months of age [63, 64]. In the neonates, renal tubular secretion can be important for the elimination of those drugs which are renally secreted (penicillins and cephalosporins). In children and adolescents, the tubular secretion capacity can even be greater than in adults. For example, when imipenem–cilastatin was given to children of 3–12 years of age, imipenem renal clearance in children was 1.95-fold greater than the estimated creatinine clearance, suggesting significant tubular secretion of imipenen in children [65].

3.5.3 Tubular Reabsorption

Tubular reabsorption is a passive process [62]. Lipid-soluble drugs readily cross the tubular membrane, but water-soluble drugs or ionized drugs are not reabsorbed [66]. The reabsorption of weakly acidic or basic drugs depends on the pH of the tubular fluids [66].

The tubular reabsorption is relatively immature at birth, especially in the preterm infants. Reabsorption of certain amino acids increases with postnatal age, but phosphate reabsorption is enhanced during the immature state. Transport system for glucose is relatively mature in infants, but in infants less than 34 weeks of gestation, it remains immature [67]. The peak maturation level may be between 1 and 3 years [68].

3.6 Measurement of Renal Function

Glomerular filtration rate (GFR) is widely used to characterize renal function across different age groups (preterm neonates to adults). The knowledge of GFR can be important for the selection of a suitable dose for exclusively renally excreted drugs [69]. GFR is generally determined by estimating the clearance of endogenous markers such as creatinine or cystatin-C, and exogenously administered substances such as inulin, mannitol, iohexol, or ^{51}Cr-ethylene diamine tetra-acetic acid (^{51}Cr-EDTA) [69]. However, determination of GFR by these markers can be time consuming and technically difficult. Administration of inulin or any other exogenous substance to neonates and young children to determine GFR can be much more difficult than older children and adults. Therefore, in order to avoid difficulties with determining GFR experimentally, equations with endogenous markers have been developed for everyday clinical use [59, 70]. These equations are intended to replace experimentally determined GFR as the use of these equations for GFR estimation saves time and effort.

Creatinine clearance and blood urea nitrogen are widely used as a measure of renal function [62]. In patients with renal impairment, reduced glomerular filtration results in the accumulation of creatinine and the degree of accumulation of creatinine is directly related to the degree of loss of glomerular filtration in the kidneys. Although creatinine clearance as a measure of renal function has been criticized, it remains the method of choice for the evaluation of renal function. Creatinine clearance can be directly measured using serum and urine creatinine concentrations. Urine should be collected until 24 h and blood for serum creatinine measurement should be collected at the midpoint of urine collection [62].

$$\mathrm{CL_{CR}} = \frac{\mathrm{CR\ urine\ conc\left(mg/dL\right)} \times \mathrm{urine\ volume\ \left(mL/min\right)}}{\mathrm{serum\ creatinine\ concentration\left(mg/dL\right)}} \tag{5.6}$$

As mentioned earlier, there are also several indirect methods to determine creatinine clearance [71]. Some formulae for indirect measurement of creatinine clearance are shown below [71]:

3.6.1 Cockroft–Gault (>12 years)

$$\mathrm{CL_{CR}} = \frac{\left(140 - \mathrm{age}\right) \times \mathrm{weight}}{72 \times \mathrm{Serum_{CR}}} \tag{5.7}$$

Creatinine clearance in females $= 0.85 \times \mathrm{CL_{CR}}$ in males obtained from Eq. 5.4.

3.6.2 Schwartz (Infants <1 Year)

$$\mathrm{CL_{CR}} = \frac{0.45 \times \mathrm{length}}{\mathrm{Serum_{CR}}} \tag{5.8}$$

3.6.3 Schwartz (Children 1–12 Years)

$$\mathrm{CL_{CR}} = \frac{0.55 \times \mathrm{length}}{\mathrm{Serum_{CR}}} \tag{5.9}$$

In the abovementioned equations, $\mathrm{Serum_{CR}}$ is in mg/dL, age in years, weight in kilograms, length in centimeters, and creatinine clearance in mL/min.

3.6.4 Modified Schwartz Equations

Over the years, Schwartz refined his equations and the following are his revised equations:

$$\text{Schwartz et al.}[72] = \mathrm{GFR} = k \times \text{height} / \mathrm{PCr} \text{ where } k = 36.5 \tag{5.10}$$

$$\text{Schwartz-Lyon}[73] = \mathrm{GFR} = k \times \text{height} / \mathrm{PCr} \tag{5.11}$$

$k = 37$ if males aged >13 years and $k = 33$ if others

where GFR is measured in mL/min/1.73 m^2, PCr is expressed in micromoles per liter, and height in centimeters.

3.6.5 Height-Independent Equation

A height-independent equation has been proposed by Pottel et al. [74] to calculate estimated glomerular filtration rate (eGFR), estimate GFR in children. The equation is as follows:

$$\mathrm{GFR}\left(\mathrm{mL/min/1.73\ m^2}\right) = 107.3 / \left(\text{Serum creatinine} / Q\right) \tag{5.12}$$

where serum creatinine is in mg/dL and Q is the median serum creatinine concentration for children based on age and sex. Q can be calculated from the following equation [75]:

$$\text{Median serum creatinine}\left(Q\right)=0.027\times\text{age}+0.2329 \tag{5.13}$$

Other Equations Some other equations that can be used to estimate GFR in children are as follows:

Creatinine-Based Counahan–Barratt Equation [76]

$$\text{GFR}\left(\text{mL}/\text{min}\right)=0.43\times\text{height}\left(\text{cm}\right)/\left(\text{SCr}\left[\text{mg}/\text{dL}\right]\right) \tag{5.14}$$

Equation According to Cystatin C-Based by Grubb et al. [76, 77]

$$\begin{aligned}\text{GFR}\left(\text{mL}/\text{min}/1.73\ \text{m}^2\right)&=84.69\times\left(\text{S}_{\text{cystatinC}}\left[\text{mg}/\text{L}\right)^{-1.68}\right.\\&\quad\times1.384\left(\text{in children}<14\ \text{years}\right)\end{aligned} \tag{5.15}$$

3.7 Chirality

Many drugs are administered as racemates and in many cases considerable differences occur between the two enantiomers resulting in different pharmacological activity and drug disposition. In recent years, there is a lot of emphasis in synthesizing individual enantiomer rather than a racemic mixture. Pharmacokinetic studies are regularly conducted both in adults (in majority of cases) and children. Some examples of pharmacokinetic studies with racemic mixtures in children are presented below.

3.7.1 Ketorolac

Kauffman et al. [78] studied the pharmacokinetics of R(+)- and S(−)-ketorolac in children (3–18 years). Based on per kilogram body weight, the authors found that the clearance of racemic ketorolac in children (1.1 mL/min/kg) was approximately two times the clearance reported in adults (0.3–0.55 mL/min/kg). Clearance of the S(−) enantiomer was four times that of the R(+) enantiomer. The clearance of S(+)- and R(−)-ketorolac in children was 6.2 and 1.4 mL/min/kg, respectively.

In a double-blind, placebo-controlled study, Lynn et al. [79] studied the pharmacokinetic of ketorolac in 37 infants and toddlers (6–18 months of age) postoperatively. On postoperative day 1, infants were randomized to receive placebo, 0.5, or 1 mg/kg racemic ketorolac as a 10-min IV infusion. Blood samples were collected up to 12 h after dosing. The $C_{\max}$ at the end of the infusion were approximately two times higher for the R(+) enantiomer compared to the S(−) enantiomer, for both racemic doses. For R(+) enantiomer, the volume of distribution of the central compartment, clearance, and half-life were 1200 ± 163 mL, 7.5 ± 0.7 mL/min, and

238 ± 48 min, respectively. For S(−) enantiomer, the volume of distribution of the central compartment, clearance, and half-life were 2320 ± 34 mL, 45.3 ± 5.5 mL/min, and 50 ± 42 min, respectively. The study indicated a shorter half-life and faster clearance of S-isomer than the R-isomer in infants and toddlers.

3.7.2 Tramadol

Bressolle et al. [80] studied the population pharmacokinetics of tramadol in 25 children (1–8 years of age). Tramadol was administered after surgery by continuous infusion (loading dose, 2 mg/kg intravenously over 10 min followed by continuous infusion of 8 mg/kg over 24 h). The clearance of R-tramadol and S-tramadol was 13.3 and 14.7 l/h, respectively. The volume of distribution of R-tramadol and S-tramadol was 25.3 and 34 l, respectively. The half-lives of both enantiomers were approximately 3 h.

3.7.3 Warfarin

Takahashi et al. [81] studied the pharmacokinetics and pharmacodynamics of warfarin enantiomers in 38 children (1–11 years), 15 adolescents (12–18 years), and 81 adult (37–76 years) patients following long-term warfarin therapy. The unbound clearance of (S)-warfarin in children, adolescents, and adults was 346 ± 217, 533 ± 285, and 637 ± 298 mL/min, respectively. After adjusting for body weight, the unbound clearance of (S)-warfarin in children, adolescents, and adults was 18.1 ± 9.2, 12.6 ± 8.1, 11.6 ± 5.4 mL/min/kg, respectively. Body weight adjustment indicated that (S)-warfarin clearance in children was almost 1.5 times higher than adults. The clearance of (R)-warfarin like (S)-warfarin increased with age, but based on body weight adjustment, the clearance of (R)-warfarin was similar in all three age groups.

3.7.4 Ibuprofen

Dong et al. [82] studied the pharmacokinetics of stereoselective ibuprofen in children with cystic fibrosis ($n = 38$, 2–13 years of age). The patients were given a single oral dose of racemic ibuprofen (20 mg/kg). Mean C_{max}, AUC, oral clearance (CL/F) of S-ibuprofen were significantly different from those of R-ibuprofen as shown in the table below. Compared to febrile but otherwise healthy children, children with cystic fibrosis had increased oral clearance for both isomers (Table 3.1).

Conclusions The studies in children with racemic compounds indicate that like adults, pharmacokinetics of these compounds are also stereoselective in children.

Table 3.1 Pharmacokinetic parameters of racemic ibuprofen to children following an oral dose of 20 mg/kg

Parameters	S-ibuprofen	R-ibuprofen
C_{max} (μg/mL)	41.1 ± 12.0	33.9 ± 12.8
AUC (μg×h/mL)	120.0 ± 59.0	58.9 ± 24.1
CL/F (mL/min/kg)	1.62 ± 0.55	3.30 ± 1.35

However, the pharmacokinetics of individual isomer may be different between children and adults as seen with nonracemic compounds. The magnitude of conversion of one isomer to another in children as compared to adults has not been established. This may be important for newborns and infants due to therapeutic and toxicity concerns.

3.8 Pharmacodynamics in Children

The effect of human ontogeny on the pharmacodynamics (PD) of drugs has not been well established. Theoretically, age-dependent variation in receptor number and receptor affinity for drugs could influence the response of drugs. There are also difficulties in measuring small but significant effects because such effects are difficult to assess in children [83]. According to Stephenson [83], the view that drug response or effect differs between adults and children mainly arise due to the lack of studies which could establish or reject this view.

Due to ethical reasons, conducting PK or/and PD studies in children has drawn opposite opinions. For example, Padbury [84] questions if pharmacokinetic and pharmacodynamic studies need to be carried out for every new drug intended to be given to neonates. On the other hand, Stephenson [83] maintains that once a large randomized and controlled clinical trial has been conducted in adults, one may not need a large pediatric population to affirm safety and efficacy. Using Bayesian statistics, pharmacodynamics, and surrogate endpoints, one can substantially reduce the sample size in pediatric population to study safety and efficacy of a drug which has been already studied in adults. Some examples of pharmacodynamic differences between adults and children are presented below:

3.8.1 In Vivo Warfarin Study

Takahashi et al. [81] measured plasma concentrations of unbound warfarin enantiomers, vitamin K1, and vitamin K–dependent proteins (prothrombin fragments 1 + 2, protein C, and the protein-induced by vitamin K absence) and international normalized ratio (INR) in 38 children (1–11 years), 15 adolescents (12–18 years), and 81 adult (37–76 years) patients following long-term warfarin therapy. The children had lower plasma concentrations of protein C and prothrombin fragments 1 + 2 and greater INR than the adults. On the other hand, pharmacodynamic properties between adolescents and adults were similar. The mean INR in children was

significantly greater than the adult patients (1.79 versus 1.58). The results of the study demonstrated that the pediatric patients might have been more sensitive to warfarin than the adult patients. Since the response of warfarin was augmented in children, the authors suggested that this augmented response to warfarin in children should also be taken into account for estimating warfarin doses for children.

3.8.2 In Vitro Cyclosporine Study

An in vitro study was conducted in 56 subjects (3 months to 39 years old) to determine the relationship between age and in vitro cyclosporine pharmacodynamics [71]. The subjects were divided into four age groups: infants (0–1 years), children (>1–4 years), pre-adolescents (>4–12 years), and adults (>12 years). The peripheral blood monocytes of the infants showed a twofold lower peripheral blood monocyte proliferation (mean $IC_{50} = 18.3$ vs. 37.4 ng/mL) and sevenfold lower interleukin two expression (mean $IC_{90} = 123$ vs. 898 ng/mL) than peripheral blood monocytes from older subjects. The three older age groups were similar with respect to peripheral blood monocyte proliferation. The authors' conclusion was that cyclosporine pharmacodynamics in vitro are related to age, and if this factor is neglected, then it may become a source of iatrogenic risk during pediatric immunosuppressive therapy.

3.8.3 Regional Hemodynamic Effect of Dopamine in Preterm Neonates

Seri et al. [85] studied the effects of dopamine on renal, mesenteric, and cerebral blood flow in 23 nonhypotensive preterm neonates (birth weight: 981 ± 314 g; postnatal age: <2 days). Dopamine was given at a dose of 6.1 ± 3.0 mg/kg per minute to manage oliguria or impaired peripheral perfusion, or both. Dopamine significantly increased blood pressure and urine output. Dopamine decreased the pulsatility index in the renal artery while the pulsatility index in the superior mesenteric and medial cerebral artery was not affected. Thus dopamine increased the renal blood flow while mesenteric and cerebral blood flow remained unchanged. The authors recommended that low doses of dopamine should not be used to augment mesenteric blood flow in nonhypotensive preterm neonates with necrotizing enterocolitis.

3.8.4 Lansoprazole

Pharmacokinetics and pharmacodynamics of lansoprazole were studied in 40 children (18 days to 14 years) [86]. The children received a single or multiple oral dose of lansoprazole (17 mg/m^2 or 17 mg/m^2 for 7–14 days). In both single and multiple

dose groups, the antisecretory effect decreased with age. The results of the study suggested that the antisecretory effect is higher in infants younger than 6 months than in older children and adults. The authors suggested that a dose of 17 mg/m^2/day may be too high in children younger than 3–4 months.

3.9 Conclusions

There are very few studies that have compared or evaluated the pharmacodynamics of drugs between children and adults. However, generalization that the response of drugs between children and adults will always differ may not be true. Furthermore, extrapolation of response for some drugs from adults to children may not be appropriate even for the same disease but one should not ignore the fact that the etiology and course of disease may be different in children from adults. Hence, not only age but the nature of disease should also be taken into account for designing a suitable dosing regimen in children. For example, the response to drugs to depression, asthma, epilepsy, and acute lymphoblastic leukemia in children may be very different than in adults. Stephenson's [83] view that once a drug has been thoroughly evaluated for adult use one may want to conduct comparatively smaller clinical trial in children evaluating the safety and efficacy of a drug is meaningful and practical. It should also be recognized that conducting a pharmacodynamic study in young children is not always feasible.

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Chapter 4
Pediatric Clinical Trial Design and Dosing

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4.1 Introduction

In the context of drug development, clinical trials are experiments that involve the administration of an intervention to human subjects and the gathering of data to assess the dosing, safety, and efficacy of the intervention. Within a given drug development program, there are many clinical trials conducted. The size, scope, and design of a clinical trial will vary depending upon what stage in development the investigational drug product is in and the research question(s) that is being answered. In early phase trials, the objectives are usually to identify an optimal dose(s) and to obtain information on the ADME properties and toxicity of the drug. The study population enrolled is often small (10–30 subjects) and may include healthy volunteers (in the case of the adult population) or subjects with the disease/condition of interest (in the case of adult and pediatric populations). In the later phases of drug development, the clinical trials progressively become of larger scale and seek to generate preliminary data followed by confirmatory data on the drug's efficacy and safety in the intended population. These trials frequently involve the inclusion of a comparator arm(s) also known as a control group.

The clinical trial protocol provides the operating instructions that govern the manner in which researchers perform the trial. The protocol states the trial objective(s) and describes the methodology, endpoints to be measured, statistical

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considerations, safety precautions, and general design of the trial. A study schema is a flowchart which provides an illustration of the design and timeline of the trial. Throughout this chapter, study schemas will accompany the discussion of various trial designs used in clinical research.

4.2 Inclusion of Pediatric Subjects in Clinical Research

The inclusion of infants, children, and adolescents in clinical trials inserts an added layer of complexity to drug development for a number of reasons, including the relatively small number of pediatric patients available for clinical trials as compared to adults, an unwillingness of parents to enroll their children in clinical trials, as well as other methodological and logistical issues. Furthermore, there are ethical principles, as described in 21 CFR Part 50, Subpart D, intended as additional safeguards for protecting children participating in clinical research since they are considered a vulnerable population [1]. Selection of a control group in pediatric trials can be more complicated than in adult trials due to the ethics around assigning a patient to a placebo arm. According to the International Conference on Harmonization (ICH) Guideline E10 on Control Groups, control groups are required to allow for "discrimination of patient outcomes (for example, changes in symptoms, signs, or other morbidity) caused by the test treatment from outcomes caused by other factors, such as the natural progression of the disease, observer or patient expectations, or other treatment [2]". In 21 CFR Part 50 Subpart D, there is no prohibition on the use of placebo in pediatric trials, but there is a requirement for minimization of risk. When there is clinical equipoise in research, both the treatment and placebo arms present similar risk levels in most cases [3]. In some specific situations, it is possible to avoid using placebo. For example, if the course of an illness is predictable and treatment regimens have not changed significantly over time, a historical control group may be appropriate. If a historical control is not possible, an active control may be an option. In an active control trial, one arm will receive the current standard of care and another arm will receive the new intervention, sometimes in addition to the current standard of care. Crossover designs, which will be discussed in more detail later in this chapter, allow individual patients to serve as their own control. These control group alternatives allow researchers to ethically draw conclusions about efficacy and safety of interventions without compromising validity of inference.

Unlike adults, children cannot consent to enroll into a trial and the allowable risk a child can be exposed to within a clinical investigation must be restricted based upon whether the intervention being studied offers the child a prospect of direct clinical benefit [4]. Therefore, children must only be enrolled in trials that are scientifically necessary and ethically sound, and whenever possible, data needed to support the safe and effective use of drug products in children should be obtained from other sources (e.g., adult populations).

4.2.1 Extrapolation in Pediatric Drug Development Programs

For drug products to obtain marketing approval from the US Food and Drug administration (FDA), it is required that the drug manufacturer demonstrate the effectiveness of their product within the context of adequate and well-controlled studies [5]. In some instances, the required substantial evidence of effectiveness to support use of a drug product in children can be based on adequate and well-controlled studies in adults [6]. This is referred to as extrapolation of efficacy from adults to the pediatric population, and it is an important means for utilizing all relevant data, decreasing the number of unnecessary trials in children, and streamlining pediatric drug development. Whether or not, and to what degree, efficacy data can be extrapolated from adult populations to pediatrics is dependent upon a series of evidence-based assumptions: (1) that the course of the disease is sufficiently similar; (2) that the response to the intervention will be sufficiently similar; and (3) that there is a sufficiently similar exposure-response relationship in adults and children [7].

The use of extrapolation can be grouped into three categories, full extrapolation, partial extrapolation, and no extrapolation, and can inform the approach to pediatric dose selection and the types of studies needed for a pediatric drug development program [8]. When there is evidence to support that the course of the disease, response to intervention, and the exposure-response relationship are all sufficiently similar in the adult and pediatric population, then full extrapolation of efficacy data from adults to children is possible. In this case, a pharmacokinetic (PK) and safety approach can be employed where a pediatric PK study is conducted to identify a pediatric dose that will achieve a systemic drug exposure similar to that determined to be safe and effective in adults. This approach to dose selection is sometimes referred to as "exposure-matching."

Partial extrapolation of efficacy is a valid approach when it is believed that the course of the disease and the response to the intervention are similar in the adult and pediatric population, but there is some residual uncertainty about whether the exposure-response relationship is the same in the two populations. In this case, a PK-pharmacodynamic (PD) and safety approach could be applied where a study is conducted to characterize the exposure-response relationship in the pediatric population, which is then compared to the exposure-response relationship previously defined in adults. This approach requires that there is a PD measurement that can be used to predict efficacy in children and a dose-ranging PK-PD study is conducted in children in order to identify a dose(s) that achieves the target PD effect. If there is not an appropriate PD marker that can be measured, then a single adequate and well-controlled trial which tests a range of doses and assesses a clinical endpoint is needed. In some instances, a single controlled or uncontrolled safety and efficacy trial (qualitative data) could be sufficient.

In the case where the disease process is unique to the pediatric population, or the disease process and response to intervention differs in adults and children, or there is limited information available to support the assumption that the disease process

and response to intervention are similar in the two populations, extrapolation of efficacy data from adults to pediatrics is not possible (i.e., no extrapolation). Hence, a full pediatric development program would be required to provide substantial evidence of effectiveness. This would involve a PK, safety, and efficacy approach where two adequate and well-controlled clinical trials, evaluating preferably more than one dose level, are conducted in pediatric subjects.

There are a few important things to note about extrapolation and the design of pediatric drug development programs: (i) Unlike efficacy data, safety data may differ between populations, and therefore, safety data cannot be extrapolated from adult populations to children. For all three approaches described above, sufficient safety information must be collected in the pediatric development program. (ii) Regardless of the extrapolation approach used (i.e., full, partial, or no extrapolation), modeling and simulation methodologies can be utilized to inform dose selection for the pediatric clinical trial(s). (iii) Extrapolation of efficacy can be from sources other than adult data. For example, efficacy data can be extrapolation from one pediatric age group to another pediatric age group, from one formulation to another containing the same active ingredient, or from related pediatric indications. (iv) Lastly, the use of extrapolation can improve the success rate of pediatric drug development programs to achieve FDA approval for pediatric use. A survey of 370 pediatric studies submitted to the FDA in response to a pediatric Written Request found that when extrapolation was used, 61 % (84 of 137) of the drug products obtained a new pediatric indication for use or extended the FDA-approved age group. When extrapolation was not used, only 34 % (10 of 29) of drug products achieved this goal [8].

4.2.2 Pediatric Trial Failures

According to a recent survey of pediatric development programs submitted to the FDA between 2007 and 2014, approximately 40 % of pediatric trials have "failed to establish either safety or efficacy, leading to an inability to label the product for use in children." While there are likely multiple reasons why a given trial may fail, a few common contributing factors include inappropriate dose selection, not accounting for differences between the adult and pediatric disease process, high placebo response, and suboptimal study design [9]. For the trials in which dosing was determined to be a contributing factor to the inability to demonstrate efficacy, the most common oversights were failing to test a range of doses in the pediatric clinical program and/or limiting the pediatric drug exposure to that which was determined to be safe and effective in adults. Momper et al. illustrate this point with the example of failed pediatric development programs for neurogenic bladder dysfunction (NBD) where the programs selected the pediatric dose based on targeting the adult drug exposure shown effective for benign prostatic hypertrophy (BPH), despite clear differences in the adult and pediatric disease [10].

4.3 Elements of Clinical Trial Design

Poor choice or execution of trial design can be a contributing factor to trial failure. Selection of an optimal trial design is complex given that trial design in the broader sense encompasses many elements such as the target population, inclusion/exclusion criteria, choice of comparator group, handling placebo response, blinding, allocation to intervention, comparison structure, hypothesis testing, efficacy endpoint selection, and timing of measurements. Here, we will highlight a few of these trial design elements. Examples of trial designs are discussed later in this chapter.

4.3.1 Study Enrichment

Determining the appropriate population for testing and demonstrating the effect of a new drug or biological product is critical in drug development. Enrichment refers to the prospective use of any patient characteristic to select a study population in which detection of a drug effect (if one is in fact present) is more likely than it would be in an unselected population [11]. Almost all clinical trials employ some form of enrichment given that trials are conducted in selected populations, and not the general population. There are essentially three main types of study population enrichment: decrease heterogeneity, prognostic enrichment, and predictive enrichment. Certain enrichment approaches are more intricate than others, but all increase the study power to demonstrate a treatment effect.

Decreasing heterogeneity is a practical approach which involves reducing the noise or variability within a trial. This can be done, for example, by including patients whose disease is stable and who have baseline measurements within a narrow range which decreases inter-patient variability. Intra-patient variability can be decreased by excluding patients whose symptoms/disease improves spontaneously or who have highly fluctuating measurements. Other strategies that fall within the category of decreasing heterogeneity include enrolling patients who meet defined criteria related to the disease being studied, selecting patients likely to comply with treatment, excluding patients unlikely to tolerate the drug or who are taking drugs that are pharmacologically similar to or could interact with the study drug, excluding patients who are likely to drop out of the trial, and eliminating patients more likely to have large placebo responses.

Prognostic enrichment refers to identifying patients that are at high risk of having the event of interest in a trial. For example, this approach works well for prevention trials where the study drug is being evaluated to reduce the rate of death or other serious event. In order to increase the power of the study to detect the level of risk reduction offered by the drug, it would be prudent to enroll patients who are most likely to have the event. The sample size that is appropriate for an event-based study is dependent upon the effect size and the event rate in the control group. It is important to note that prognostic enrichment does not change the relative risk reduction. In other words, the study group does not necessarily have a greater effect from the

drug since prognostic enrichment does not impact the percent of responders or percent improvement in symptoms. However, it does increase the absolute effect size (since the study group had more events within the trial), which allows for a smaller sample size.

Prognostic enrichment can also be used to select patients with more rapid progression of their disease/condition for studies of drugs intended to delay disease/condition/progression or select patients with high baseline disease severity. For example, the clinical development program for omalizumab (Xolair®) for the treatment of chronic idiopathic urticaria (CIU) enrolled patients 12 years of age and older who had a diagnosis of CIU for 6 months or more and suffered 8 consecutive weeks of itching/hives at any time prior to enrollment despite current use of approved doses of H1 antihistamines.

Identifying a patient population that is more likely to respond to the study drug is considered predictive enrichment. There are a variety of ways of selecting patients more likely to respond, such as selecting patients based on a past history of response to the drug or drug class, on a proteomic or genomic marker related to the drug's mechanism of action, or on a specific aspect of the disease pathophysiology. Since predictive enrichment can lead to observing a larger effect size (both absolute and relative) within the trial, it allows for the use of a smaller trial sample size. An example of predictive enrichment can be illustrated by the clinical development program for a new dosage form of oxybutynin (extended release [XL] tablets) in children with detrusor overactivity associated with a neurological condition. This program consisted of two open label studies, one of which was a 24-week safety and efficacy study in children 6–15 years of age and the other which was a pharmacodynamics study in children 1–5 years of age. In both studies, all patients enrolled were current users of oxybutynin and had a history of tolerating and responding to the medication. Prior to baseline evaluations at the start of the study, a minimum washout period of 3 days was required.

In some cases, enrichment strategies can allow for the individualization of therapy. However, regardless of the enrichment strategy employed, it is important to consider the generalizability of results from studies involving enriched populations. Important questions to consider include: Are the results applicable to populations who do not have the enrichment characteristic, and how much data should be obtained in populations without the enrichment characteristic? [12]

4.3.2 Endpoints: Biomarkers and Clinical Outcomes

An important consideration for designing a clinical trial is the choice of endpoint(s) or outcome(s) to be measured. For trials intended to demonstrate drug efficacy as part of a drug development program, the selection of an appropriate primary efficacy endpoint(s), which is well-defined, measurable, reliable, and interpretable, is an important element for trial success. Endpoints can be categorized as objective (e.g., survival, a laboratory measurement, disease exacerbation, or clinical event) or subjective (e.g., a symptom score/scale or a quality of life measurement). A

clinically meaningful endpoint is an endpoint that directly measures how a patient feels, functions, or survives. A biomarker is a characteristic that is objectively measured (e.g., laboratory measure or physical sign) and evaluated as an indicator of normal biological processes, pathogenic processes, or biological responses to a therapeutic intervention [13]. A surrogate endpoint is a biomarker intended to be used as a substitute for a clinically meaningful endpoint. In order to truly be considered a surrogate endpoint, any changes in the surrogate caused by the study drug should also reflect changes in the clinically meaningful endpoint [14]. There are many examples where validated surrogate endpoints have been accepted by regulatory authorities as substitutes for clinical endpoints as a basis for drug approval, such as blood pressure lowering effects for antihypertension agents, reduction of LDL cholesterol for cholesterol lowering drugs, and CD4 count and viral load effects of antiviral drugs for treatment of HIV-1 infection [5].

4.3.3 Clinical Trial Simulation

Careful planning in regard to the approach to dose selection and the ideal trial design can greatly improve the probability of success of a clinical trial. Model-based clinical trial simulation (CTS) is the use of mathematical models to study drug effects in virtual patient populations. CTS can be a powerful tool for study planning by predicting the impact of various factors (e.g., patient dropout, placebo response, and endpoint variability) on trial outcome and can provide predictions of the probability of trial success (i.e., the probability that the trial will show a positive outcome in determining clinical benefit) in the context of differing scenarios [15, 16]. Depending on the type of model used, these models can incorporate all relevant knowledge and describe the biological system and disease pathophysiology, drug disposition, or the operating characteristics of a trial [17]. For example, Knebel et al. describe a model and simulation exercise intended to integrate the information collected on the nonstimulant drug guanfacine and other drugs for treating attention deficit hyperactivity disorder (ADHD) in order to describe the exposure-response relationship, placebo time course, and dropout pattern in ten pediatric ADHD trials [18].

CTS affords the ability to test assumptions prior to the design of the clinical trial and can be particularly valuable in informing the selection of an optimal and efficient design for a pediatric clinical trial given the limitation of feasibly being able to physically test multiple hypotheses due to small patient populations [19]. Simulations have the potential to investigate the causal factors of and prevent future trial failures [20–22], reduce the number of patients needing to be studied in the actual trial, gain greater certainty in the endpoint(s) to be assessed, and determine the best combination of trial elements to incorporate into a given trial all while improving efficiency in drug development [23].

4.4 Efficient Trial Designs

Efficient trial designs can assist with overcoming some of the previously discussed barriers failed trials faced. For example, in the case of high placebo response in pediatric patients, when using adapted three-stage trials, placebo responders exit the study while the trial maintains statistical power. When dealing with small numbers of subjects, adaptive, crossover, early escape, and N of 1 designs allow researchers to maximize the amount of useful information obtained. In the case of study design issues, efficient trial designs offer innovative ways to safely and ethically prove efficacy.

In addition to the barriers already mentioned, pediatric clinical trials must also operate with ethical constraints and logistical obstacles. As a result, more efficient trial designs must be strategically considered. An overview of various efficient trial designs follows.

4.4.1 Crossover Design

In the crossover design, each subject sequentially receives both interventions being compared as seen in Fig. 4.1 [24]. Familial Mediterranean fever (FMF) is a rare autoinflammatory disease with limited treatment options characterized by recurrent attacks of fever, peritonitis, pleuritis, and arthritis. A trial of rilonacept employed a crossover design to look at a primary endpoint of frequency of FMF attacks. Approximately 17 enrolled subjects 4 years of age or older alternated between rilonacept (R) and placebo (P): RPRP, PRPR, RPPR, and PRRP in treatment courses 90 days in length [25]. It is important to note that the interventions are separated by a washout period that must be of sufficient length to prevent confounding of results due to carryover of drug effect between interventions. The risk of carryover is a major disadvantage of this design and makes it inappropriate to use in drugs with a long half-life. Each subject serving as his or her own control is a major advantage of this trial design. Greater precision in results can be expected since variation within a single subject's response will be lower than variation of responses between different subjects. When performing a crossover trial, a smaller number of subjects are required as compared to a parallel group design and yet still results in the same power to analyze outcomes. In subjects with stable, chronic disease states where recruiting is a problem, this gives the crossover design an advantage [26, 27]. It logically follows then that this trial design would not be appropriate in unstable disease states with spontaneous improvement.

The FMF trial highlights a second disadvantage of the crossover design, exposure to inferior treatment. In crossover designs with more than two periods in which the subject alternates between active treatment and placebo more than once, ethical questions can arise about exposing subjects to placebo. However, the crossover design can be further modified to minimize exposure to inferior treatment while maintaining statistical significance by using the early escape design.

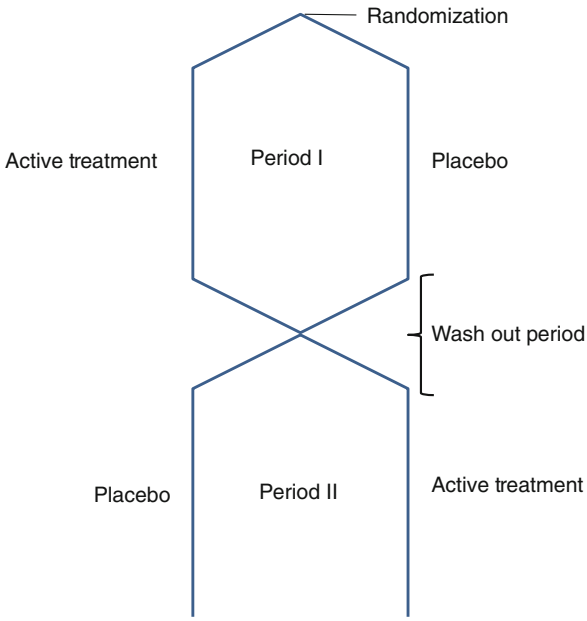

Fig. 4.1 Crossover design (American College of Clinical Pharmacology website. http://accp1.org/pharmacometrics/theory.htm. Accessed 12 Oct 2015)

4.4.2 Early Escape Design

In small trials of rare diseases, dropouts due to lack of efficacy can affect the validity of the trial. Instead of requiring a subject to drop out, an early escape trial would allow the subject to choose to escape from their assigned treatment to the comparison treatment for the remainder of that treatment period after a prespecified lack of improvement or disease flare. Alternatively, the protocol could define a level of lack of improvement at which a subject would be compelled to switch blinded treatment arms. Returning to the FMF example, after suffering two episodes of FMF within a 90 day treatment period, subjects could chose to escape from their assigned treatment arm to the comparison treatment arm for the remainder of that treatment period while maintaining the blind. They would then resume the normal treatment plan starting at the next scheduled period. In this way, both minimization of exposure to inferior treatment as well as statistical power can be preserved. Expert statistical support would be required as these trials require complex statistical methodology [25, 28].

4.4.3 N of 1

The N of 1 trial is a type of cross over design which involves only one subject participating in any amount of treatment and placebo phases. There is a similar need here to have a wash out phase to prevent carry over from one treatment phase to the

next. As an advantage, this design is the pinnacle of personalized medicine with the disadvantage of limited generalizability [27, 29]. An N of 1 study of melatonin included six different pediatric patients with intellectual deficits and fragmented sleep. Participants alternated between 2-week placebo or melatonin treatment intervals for a total of 10 weeks of blinded treatment. Results showed that melatonin at a dose of 0.5 or 1 mg did not lead to differences in average sleep per 24 h, number of arousals per night, or number of nights without arousals. The authors state that this trial type was especially powerful for these patients because of the heterogeneity of the intellectual deficits and sleep disorders among patients [30].

4.4.4 Randomized Withdrawal Design

The randomized withdrawal trial is an enrichment technique in which a drug is tested in a group of subjects and those not responding to the drug exit the trial as shown in Fig. 4.2 [31]. It goes forward by re-randomizing those subjects responding to the drug. The active treatment is replaced with placebo in a subset of subjects and efficacy is determined based on the comparison of this newly introduced placebo group to the active treatment group. In this way, exposure to placebo is minimized which is an important ethical consideration and also makes it an attractive design to subjects [32]. The study of Kapvay (clonidine) for attention deficit hyperactivity disorder (ADHD) in children 6 years and older is an example of a randomized withdrawal trial. Subjects who completed the open label 4-week dose optimization and the 6-week dose maintenance phases were randomized into the 26 week double blind placebo withdrawal phase with a primary endpoint of treatment failure. This was defined as $\geq$30 % increase in ADHD Rating Scale IV (clinician version) total score and $\geq$2 point increase in the Clinical Global Impressions Scale-Severity at any two consecutive visits. There were 253 patients enrolled at the start of the 4-week dose optimization. That number dropped from 225 to 136 by the end of the 6-week maintenance phase. A withdrawal rate of 13 % during the 6-week maintenance phase was attributed to nonresponse to Kapvay. About 46 % of subjects on active drug experienced treatment failure while 63 % of subjects on placebo failed treatment, a statistically significant difference [33].

Early escape designs may be advantageous compared to a randomized withdrawal design. The randomized withdrawal design's reliance on response prior to randomization may overestimate treatment effect. In a randomized withdrawal trial, subjects are randomized to placebo or treatment only after achieving response. In an early escape design, all subjects are randomized from the beginning of the trial regardless of response and allowed to escape to an alternate arm when prespecified improvement criteria are not met or a disease flare occurs.

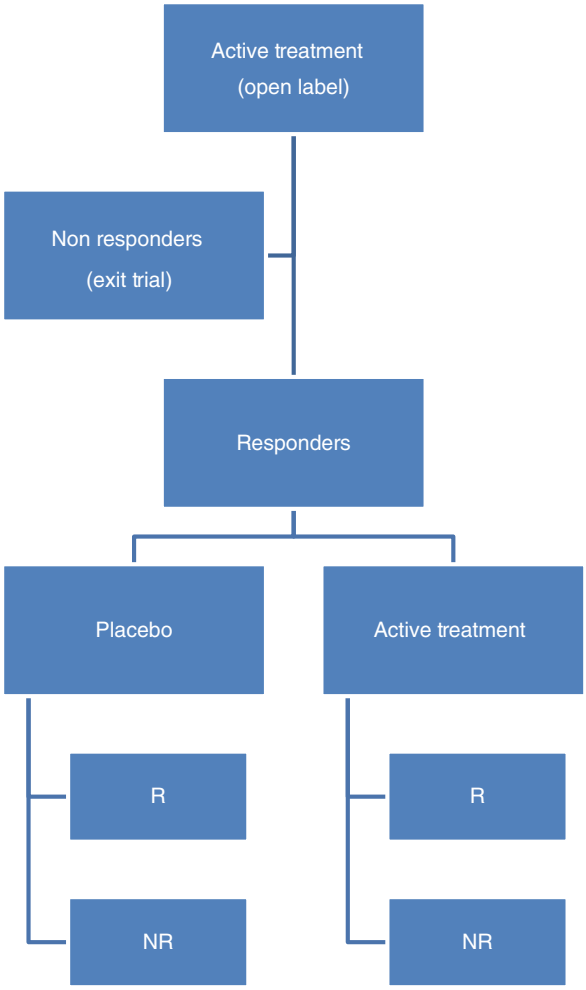

Fig. 4.2 Randomized withdrawal (Della Pasqua et al. [31])

4.4.5 Adaptive Designs

Allocation of subjects is often equivalent in each arm of a trial but it is possible to allocate subjects in an unequal fashion which is useful in minimizing exposure to placebo. For example, instead of a 1:1 allocation, 2:1 or 3:1 allocation could be used. Adaptive designs go a step further by changing subject allocation as new information is learned during the trial. Adaptive designs offer many options based on new information learned during the trial including changing inclusion criteria, dosing, sample size, and stopping the trial based on efficacy, harm, or

futility of treatment. The main advantage of adaptive designs is that they retain statistical validity despite trial design changes in real time based on learnings from the trial itself. Using an adaptive design successfully requires an endpoint that is short term and that can be measured frequently. In these trials, expert statistical support is recommended due to complex statistical methodology required [34, 35].

Group sequential design is related to adaptive design and can be useful when sample sizes are limited. Subjects are enrolled in a trial and a prespecified endpoint is determined. Based on that endpoint, either superiority of one treatment over another is declared or an additional group of subjects is enrolled in the trial until either superiority is determined or the prespecified number of groups has been exhausted. Statistical validity is maintained because each individual group analysis makes up one proportion of the total Type I error allowed [32, 34]. Brown et al. summarize by saying, "A highly significant finding is required to stop the trial at the first planned interim analysis and a less significant finding required to stop the trial based on succeeding interim analyses [36]." Toxicity could also be used as a prespecified endpoint. A safety and pharmacokinetics study of 77 patients receiving micafungin used grade 3 or greater toxicity according to National Cancer Institute Common Toxicity Criteria as the prespecified endpoint. The toxicity had to occur in at least two patients at the same dose level and be at least likely related to micafungin to stop the trial. Enrolled subjects aged 2–17 years with febrile neutropenia were treated with escalating doses of micafungin until the dose-limiting toxicity criteria were met. No dose-limiting toxicities were observed in the study [37].

In adapted three-stage design, groups are also sequential and statistical significance values can be determined for each of the three stages. This design has the advantage of removing placebo responders from the trial. Initially, subjects are randomized to active drug or placebo arms. Placebo responders exit the trial and the remaining subjects from the placebo group are re-randomized to active treatment. Subjects responding to treatment with the active drug are re-randomized to a randomized withdrawal trial. Subjects not responding to active treatment receive a prespecified dose escalation as shown in Fig. 4.3 [27, 31].

4.4.6 Stepped Wedge Design

In the stepped wedge design, all subjects receive treatment following a period of time on placebo (Fig. 4.4). These trials can be very long compared to parallel group comparisons due to the varied time on placebo prior to starting active therapy. This can be a disadvantage and skew trial results if standard of care treatments improve or change over the lifetime of the trial. A stepped wedge trial of hepatitis B vaccination in approximately 120,000 infants in Gambia was published in 1987.

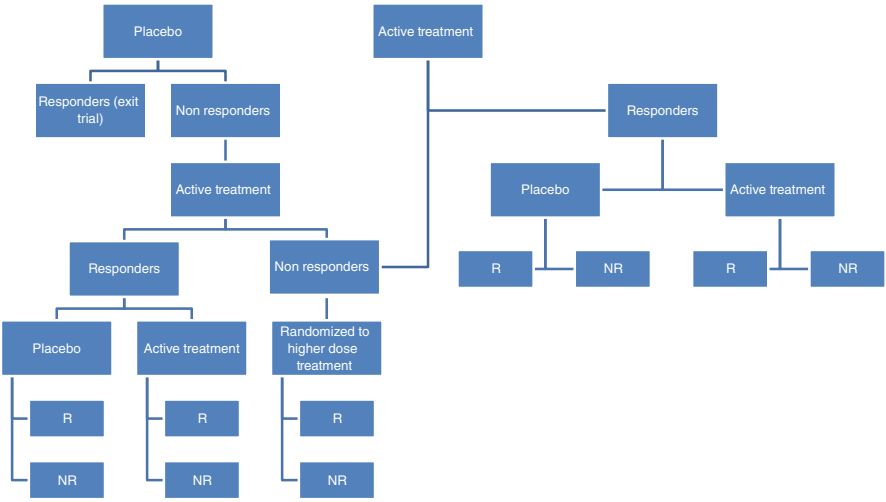

Fig. 4.3 Adapted three stage design (Della Pasqua et al. [31])

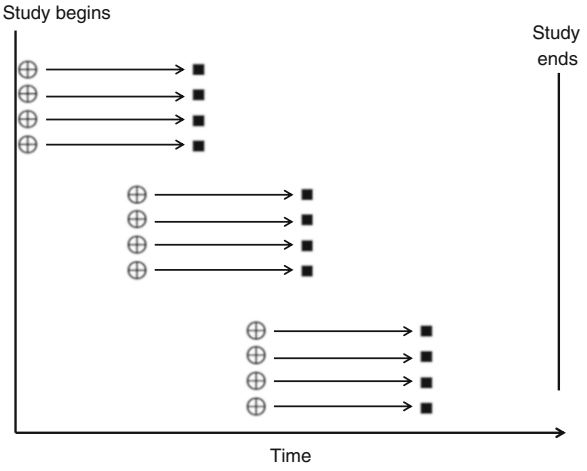

Fig. 4.4 Stepped wedge design: each line represents a patient with the circles representing the start of active treatment. The square represents the response at follow-up (Della Pasqua et al. [31])

The design came about because there were not enough resources to implement the vaccine program in all 18 health districts in Gambia simultaneously so the vaccine implementation was randomized in 10–12-week intervals. Outcomes measured included both hepatitis B virus antibody as well as incidence of liver cancer and other liver disease as endpoints. A 2014 publication showed the current prevalence of hepatitis B infection, based on the presence of hepatitis B virus antibody, in Gambia to be 0.8 % in those receiving the vaccine as children and 12.4 % in unvaccinated patients [38]. Implementing the vaccine in steps was less resource

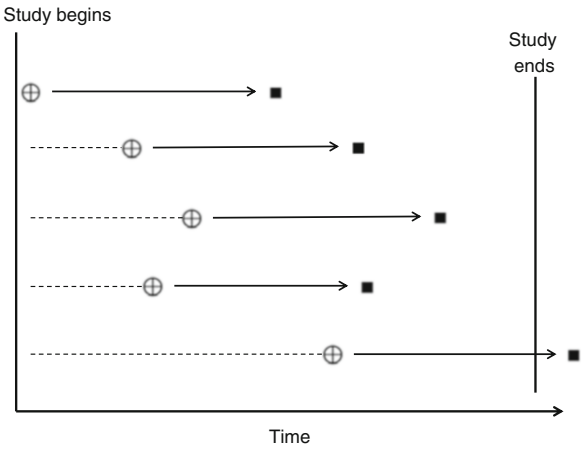

Fig. 4.5 Randomized placebo phase design: each solid line represents a patient. The dashed line represents placebo treatment with the circles representing the start of active treatment. The square represents the response at follow-up (Della Pasqua et al. [31])

intensive, which gives the stepped wedge design a definite advantage. However, the trial length was much longer than it would have been if all subjects had been vaccinated simultaneously [39, 40].

The randomized placebo phase design is a variation on the stepped wedge and is useful when studying disease-modifying therapies, for example, rheumatoid arthritis. Instead of randomization to active or placebo treatment, all subjects receive active treatment at some point during the trial but first are randomized to various lengths of time on placebo prior to starting therapy as shown in Fig. 4.5 [31]. To demonstrate efficacy, treatment for subjects on placebo for longer periods of time should have longer times to response and vice versa for subjects on placebo for shorter periods [27].

4.4.7 Concentration Controlled Design

The concentration controlled design randomizes a subject to a concentration range instead of to a specific dose. This design requires monitoring under steady-state conditions using sparse sampling and allows for more exact study of the exposure-response curve [41]. A study in approximately 50 efavirenz-naïve HIV-positive patients had a primary objective of determining dosing for efavirenz as well as evaluating the safety and virologic responses of efavirenz in combination with nelfinavir and at least one nucleoside reverse transcriptase inhibitor. Subjects aged 3–16 years were randomized to achieve AUC values previously shown to be safe and associated with virologic response in adults. AUC_{24}, Cmin, Cmax, and CL/F were measured at weeks 2, 6, and 56. The data showed that children clear the drugs faster than adults and doses were increased

after the week 2 data were obtained. Additionally, clearance increased over the course of the study, 37 % in the case of efavirenz and 62 % for nelfinavir. The authors state in their discussion, "A comparison of pediatric antiretroviral therapy studies found that those in which doses were adjusted based on measured concentrations of antiretroviral drugs resulted in superior virologic responses compared with those that used fixed-dose regimens" [42].

4.4.8 Opportunistic Design

In opportunistic trials, the use of standard of care treatments is exploited to gain additional information on understudied drugs. Parents of patients administered a drug of interest are approached for consent to allow PK sample draws that coincide with routine lab draws. Sparse sampling of multiple patients can then be used to create a population PK model. This trial design offers several advantages. When evaluated against 21 CFR Part 50 subpart D Additional Safeguards for Children in Clinical Investigations, targeting standard of care drug use and PK sample draws at the time of routine lab draws confers minimal study-related risk. Scavenged sampling, which is the use of blood/plasma remaining after testing for the purpose of medical care, confers no risk to trial subjects and increases rates of parental consent. One disadvantage of this trial design is that proper sample handling and drug stability become critical variables as the samples age. Mishandling can negatively affect the accuracy of the data if not accounted for in trial design [43, 44]. An opportunistic trial looked at clindamycin use in neonates to adolescents for *Staphylococcus* skin and skin-structure infections, intra-abdominal infection, and pneumonia. Using 194 plasma PK samples from 125 subjects, the investigators were able to create a population PK model that accurately predicted clindamycin levels in pediatric patients [45, 46].

4.4.9 Basket and Umbrella Trials

These oncology trial types use a "master protocol" format in which there are common screening assays, eligibility criteria, treatment, and statistical procedures as well as endpoints across a national network of participating study sites. This opens trial eligibility to a wider group of patients who might otherwise be unable to participate. Umbrella trials focus on a single histology type, for example, lung cancer, and assign patients to different molecularly targeted drugs based on biomarkers discovered during screening as shown in Fig. 4.6 [47]. Subtrial enrollment is limited

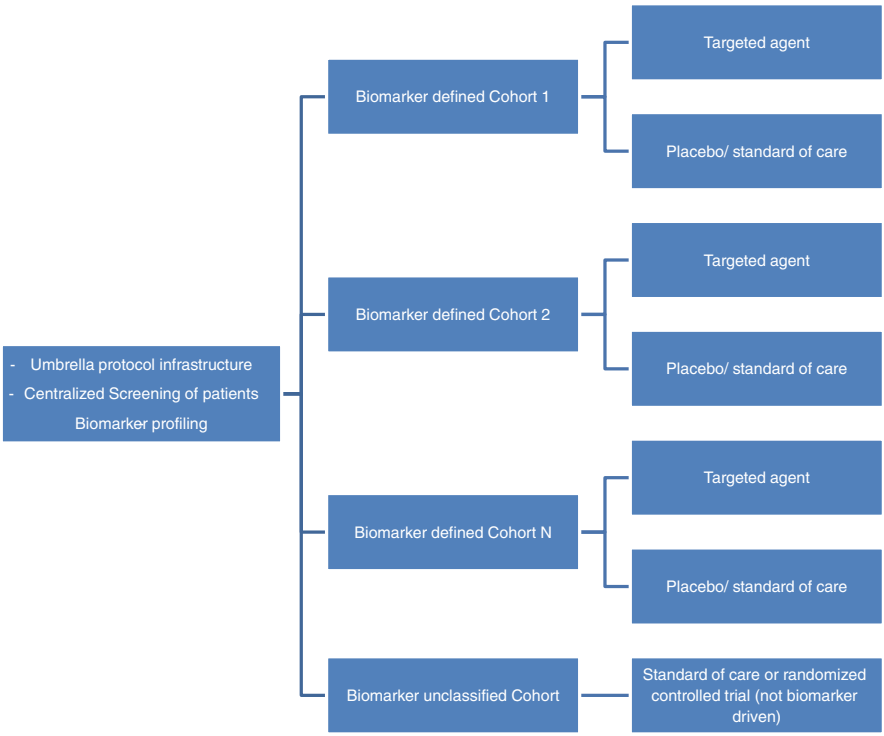

Fig. 4.6 Umbrella trial design (Mandrekar et al. [47])

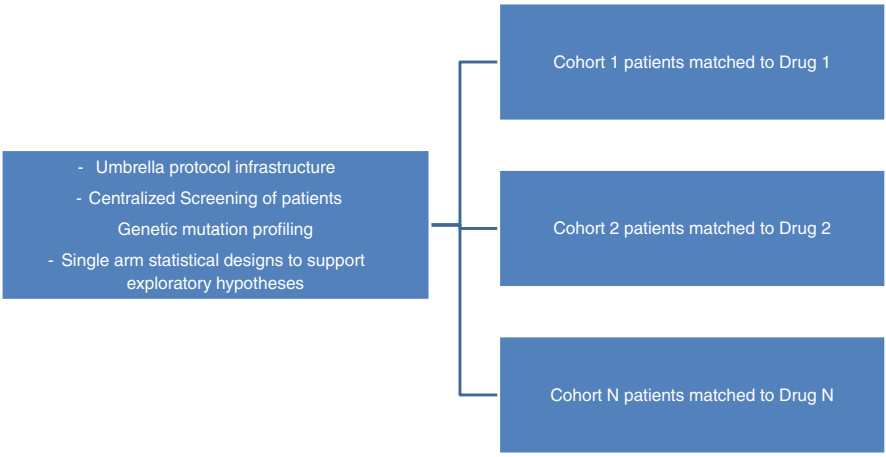

Fig. 4.7 Basket trial design (Mandrekar et al. [47])

to patients with tumors including a prespecified genomic alteration in a gene. An example of this trial type is the Lung MAP (Master Protocol–phase II/III Biomarker-Driven Master Protocol for Second Line Therapy of Squamous Cell Lung Cancer). To be eligible for this study, patients must have failed one previous treatment. Subjects were screened for prespecified genomic alterations in over 200 genes and assigned to one of four drug subtrials based on which of the test drugs will target that genetic anomaly. There is a fifth arm for patients whose tumor genotype does not match with any of the drugs under test. Basket trials expand eligibility to include all histology types but require a prespecified tumor genotype as shown in Fig. 4.7 [47]. To qualify for this trial type, a patient must have a tumor that contains, for example, EGFR mutations. These trial designs are especially useful when screening new drugs in earlier phases of development. The Molecular Analysis for Therapy Choice (MATCH) trial is an example of a basket trial. Patients with refractory tumors of any histology type were genetically screened by a common platform. They were then randomized among 20–25 subgroups treated with agents appropriate for a specific driver oncogene [47].

4.5 Summary

Despite the challenges involved in including pediatric patients in clinical research, the imperative to develop and provide safe and effective drugs for use in pediatric patients is clear. Since children are a protected population, it is particularly critical that the clinical trials they are enrolled in are ethically and scientifically sound. Planning pediatric drug development programs should involve careful consideration of the applicability of extrapolating efficacy from other populations (e.g., adults), the selection of appropriate endpoints, identifying a population in which a treatment effect can be demonstrated (e.g., study enrichment), and the determination of the best and efficient trial designs to be employed (e.g., clinical trial simulation). Well-designed and well-executed clinical research involving children is essential to improving the health of children in the USA and worldwide.

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Chapter 5
Application of Allometric Principles in Pediatric Drug Development

Iftekhar Mahmood

5.1 Introduction

Animals exist in a wide variety of shapes and sizes. Their body mass from the smallest unicellular organism to the largest multicellular animal ranges from 10^{-15} to 10^{5} kg [1]. Despite this difference in body mass, there is, however, a regular pattern in physiological process(s) which relate to body mass. This observation led the physiologists and pharmacologists to establish a relationship between body mass and physiological process(s).

In 1838, Sarrus and Rameaux developed their theory of "surface law" for the energy metabolism rates of mammals [2]. Sarrus and Rameaux demonstrated that the surface area of an animal is proportional to two-thirds power of the body mass [2].

$$S = aM^{2/3} \tag{5.1}$$

where S is the surface area, a is constant, and M is the body mass.

Since basal metabolic rate (BMR) is proportional to body surface area, Eq. 5.1 can be written as follows:

$$\text{BMR} = aM^{2/3} \tag{5.2}$$

According to Chappel and Mordenti [2], Huxley and Tessier in 1936 coined the word "allometry". Allometry is the study of size and its consequences [3, 4]. In allometric system, the proportions are altered in a regular manner. In essence, this change in a specific parameter correlates with differences in size of the organism. It

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is now well known that many physiological processes and organ sizes exhibit a power-law (not to be confused with quarter-power law) relationship with the body weight of the species. This relationship is the scientific basis of allometric scaling.

Allometric equations represent qualitative trends over orders of magnitude of body weight and provide a method to estimate or predict a physiological process (blood flow, creatinine clearance, heart rate, liver weight, kidney weight, and glomerular filtration rate, etc.) of several species including humans.

The simple allometric relationship has been shown to relate body size with a parameter of interest in the field of physiology, ecology, paleontology, and pharmacokinetics. These relationships are related to a power function or an exponent which can be as diverse as the aforementioned fields. The allometric equation relating body weight with a parameter of interest can be described as follows:

$$Y = aW^b \tag{5.3}$$

where Y is the parameter of interest, W is the body weight, a and b are the coefficient and exponent of the allometric equation, respectively.

The log transformation of Eq. 5.3 is presented in Eq. 5.4:

$$\log Y = \log a + b \log W \tag{5.4}$$

where log a is the y-intercept, and b is the slope.

Extrapolation of animal data (interspecies scaling) to predict pharmacokinetic parameters in humans has become an important tool during drug development. This extrapolation is helpful in facilitating the process of dosing transitions from animals to humans and accelerating the drug testing and approval process. Interspecies allometric scaling is based on the assumption (a correct assumption) that there are anatomical, physiological, and biochemical similarities among animals, which can be described by mathematical equations [3, 4]. Equations 5.3 or 5.4 has been extensively used to predict pharmacokinetic parameters such as clearance, volume of distribution, and half-life from laboratory animals to humans [3]. Allometric principles can also be applied within species (intra-species scaling) mainly to relate age-associated physiological, pharmacological, and pharmacokinetic differences. This chapter highlights the application of allometric principles to the pediatric drug development and prediction of pharmacokinetic parameters in pediatric population (from preterm neonates to adolescents).

5.2 Historical Background of Allometry and Allometric Exponents

The proposal of Sarrus and Rameaux [2] that the surface area of an animal is proportional to two-thirds power of the body mass became very popular and gained so much momentum that any data that disagreed with the surface law were either

rejected or assumed to be incorrect. Recent works, however, have shown that not all physiological parameters are proportional to surface area and body weight is a better representative of size for many physiological parameters than body surface area. It should be recognized that Sarrus and Rameaux exponent of 0.67 is correct for the data they utilized in their analysis.

5.2.1 Relationship Between Body Size and Basal Metabolic Rate

Over the years, allometric relationships have been established between body size and organ weights as well as between body size and physiological process(s). The exponents of these allometric relationships widely vary because allometric exponents are data dependent hence are not universal. One of the most discussed and controversial allometric relationships is between body size and basal metabolic rate (BMR) among mammals. The controversy is whether or not there is a universal exponent for basal metabolic rate. Some believe that there is a universal exponent for basal metabolic rate whereas others disagree.

5.2.2 Theory of Max Kleiber

In 1932, Max Kleiber [5] in his article, "Body Size and Metabolism," investigated the basal metabolic rates in mammals. Kleiber expressed metabolic rate (P_{met}) as a function of body mass (M) and his allometric equation was as follows:

$$P_{\text{met}} = 74.1 \times M^{0.739} \tag{5.5}$$

In 1947 [6], Kleiber published another work using 13 groups of animals (26 data points) to relate metabolic rate with body mass (in this analysis, Kleiber did not include BMR data from his 1932 study). The animals were matured, in post-absorptive condition, and at rest. From this data set, Kleiber obtained the following equation:

$$P_{\text{met}} = 67.6\, M^{0.756} \tag{5.6}$$

Further works by Brody et al. [7] and Brody [8] led to the conclusion that the basal metabolic rate as a function of body weight was proportional to 0.73.

Back extrapolation of data, however, showed large deviations in the observed and predicted BMR values for individual species. Despite the weakness of the model (deviations for individual species from observed and predicted values and lack of validation from external data), the concept of 0.75 as a universal exponent

for basal metabolic rate was accepted and became popular (Kleiber himself never maintained that the exponent 0.75 for BMR was universal).

Like Sarrus and Rameaux's proposal, Kleiber's view also became very popular and any theory or suggestion that disagreed with the exponent 0.75 was promptly discarded. Heusner [9] states that "Kleiber's search for a mass-independent metabolic rate has led to an equation where there is no room to express the metabolic effect of structural and functional differences in mammals of different sizes. This search for uniformity where it does not exist in nature has led to a theoretical impasse and has failed, to open new avenues for experimentation."

Heusner [9] was the first who challenged the concept of a universal exponent for BMR. In 1982, he suggested that the exponent 0.75 in Kleiber's equation was a statistical artifact. He mentioned that Kleiber, Brody, and others assumed that the coefficient "a" of the allometric equation ($y = aW^b$) was same irrespective of the size or species. Based on his own analysis, he noted that the magnitude of the coefficient "a" changed with both body mass (from small to large animals) and the animal species. For example, there was a threefold increase from mice to cattle. Heusner also suggested that the lines of different slopes and intercepts could not be realistically described by a single regression line and application of a single regression line was only possible to those data sets which have the same slopes and intercepts. These important and mathematically correct observations of Heusner have been completely ignored by the proponents of exponent 0.75.

In another study, Heusner [10] analyzed the relationship between basal metabolic rate and body weight in 117 dogs. Based on body weight, two different exponents for BMR were observed. For body weight, 3.2 kg or less the exponent of BMR was 0.634 and for body weight >3.2 kg the exponent of allometry was 0.869. Both these exponents were statistically significant than the exponent 0.75. Heusner concluded that in mammals, the relationship between basal metabolic rate and body weight was not accurately described by a single regression line and the commonly accepted 0.75 exponent was not applicable to the prediction of basal metabolism in dogs and mammals.

Like Sarrus and Rameaux exponent of 0.67 for body surface law, Kleiber's BMR data (published in 1947) do indicate that the exponent of 0.75 for BMR is correct. The controversy is whether or not the exponent 0.75 for BMR is universal.

Hayssen and Lacy [11] outlined several deficiencies in Kleiber's data based on which one could not assume that the exponent of BMR is universal.

- Kleiber used a very small and unrepresentative subset of animal data. Nine out of 13 species in Kleiber's data were domestic animals living under artificial energetic constraints, and there were only three primate species including humans.
- Kleiber also used multiple data points for the same species; for example, six values for rabbits, four for dogs, three cows, three women, and two for sheep. According to Hayssen and Lacy, this violates the assumption of statistical independence of the samples.
- Hayssen and Lacy used mass-specific basal metabolic rate (basal metabolic rate/mass) and found that the exponent was –0.30 and was significantly different than

Kleiber's exponent of −0.25 (basal metabolic rate/mass). Many of the species deviated from the model; for example, 21 % of the species had basal metabolic rate more than 50 % above or below the predicted values. Hayssen and Lacy's conclusion was that no single exponent could describe the allometric relation between body mass and basal metabolic rate.

5.2.3 *Theory of West, Brown, and Enquist (WBE Model)*

In 1997 [12] and 1999 [13], West et al. published two manuscripts that provided a theoretical basis for the exponent 0.75 for basal metabolic rate. West et al. used dimensional analysis, nutrient-supply networks, and four-dimensional biology to put forward their theory that a vast majority of organisms exhibit scaling exponents very close to 0.75 for metabolic rate and to 0.25 for internal times and distances.

These two publications of West et al. [12, 13] initiated a debate. In recent years, WBE model has been heavily criticized [14–35]. Many investigators noted that West et al. proposed model is not only based on questionable or unsubstantiated assumptions but is also mathematically incorrect [25–29]. West et al. model lacks an ontogenetic perspective. Further analysis of the West et al. model indicated that the model may not predict a scaling slope of 0.75, but other slopes such as 0.67, 0.81, 0.86, or 1 are possible [29–32]. Furthermore, assumption of West et al. that the biological system is fractal remains unproven [24]. Bokma [24] argues that "biological networks are not true fractals that break an organism into smaller but self-similar structures." Overall, WBE model has been found to be even theoretically incorrect and does not reconcile with observations.

5.2.4 *Savage et al.*

Savage et al. [36] analyzed metabolic rate from 626 species and found an exponent of 0.712 (95 % confidence interval: 0.699–0.724). The confidence interval excluded both 0.67 and 0.75. However, the authors considered this analysis biased because there were 477 species which weighed <1 kg whereas 149 species weighed >1 kg. Therefore, in order to minimize this bias, the authors binned the data, and after obtaining a uniform distribution, the slope was 0.737 ($n = 52$, 95 % confidence interval 0.711–0.762). The 95 % confidence interval included 0.75 and excluded 0.67. The authors concluded that they found more support for an exponent of 0.75 than of 0.67. This study by Savage et al. indicates their bias in data analysis and it seems that the authors (two of the authors in this study were West and Enquist) were determined to demonstrate that exponent 0.75 was a realistic and a universal exponent.

However, Savage et al. [31] appeared to change his views regarding WBE model. He wrote that when they computed analytical expressions for the finite-size corrections to the 3/4 exponent, it resulted in a spectrum of scaling exponents as a function

of absolute network size. When accounting for these corrections over a size range spanning the eight orders of magnitude observed in mammals, the WBE model predicted a scaling exponent of 0.81, seemingly at odds with data. The authors suggested that the current WBE model needed amendments to bring its predictions fully in line with available datasets.

5.2.5 Conclusions

The exponent of basal metabolic rate of 0.75 was first obtained by empirical data analysis by Kleiber and later a theory was built around it. Those who became the proponent of Kleiber's exponent of 0.75 never questioned about the quality of data and the number of species included in his analysis. Then the general tendency became to theoretically prove (by any means) that the exponent 0.75 is a true universal exponent for basal metabolic rate and any evidence against it was discarded with rigidity. West et al. theoretical works are generally cited by the proponents of exponent 0.75 for basal metabolic rate without recognizing that there is a lot of criticism of West et al. theory.

The current analyses of many investigators who are experts in the field (theoretical biology) suggest that the theoretical concept of exponent 0.75 for basal metabolic rate is not a real universal exponent. Although Kleiber's exponent 0.75 was derived from a small data set and is a true observation, it cannot be generalized. When large data sets were used, the notion of a universal exponent of 0.75 disappeared. The exponents of allometry are data dependent; hence, the exponents of allometry widely vary. In other words, the exponent 0.75 could have been different had Kleiber used more data in his analysis as later shown by many investigators [14–35].

In short, all investigations in search of a universal exponent for metabolic rate, done over the last 30 years, have come out empty handed and now there is a very strong evidence that "there is no universal exponent for basal metabolic rate." Theoretical allometry remains a "theory without any data support and of any practical value." A theory must be backed by evidence and this evidence is nonexistent for WBE model or any other theory which supports a universal exponent for basal metabolic rate.

5.3 Prediction of Pharmacokinetic Parameters in Children

Children are not small adults because besides body size there are biochemical and physiological differences between adults and children. Therefore, extrapolation of pharmacokinetic parameters or dose in pediatric population simply based on body weight (a linear function) from adults may lead to serious prediction error both in pharmacokinetic parameters and dosing.

Ontogeny is defined as "the history of the development of an individual from the fertilized egg to maturity" [37]. The concept of relating physiological parameters as a function of body weight has been termed by Gould [37] as "ontogenetic allometry." At least for the first decade of life, physiological changes occur rapidly, but these changes are not a linear process. Dosing in pediatric population based on body weight or body surface area without considering the developmental growth is inappropriate because body weight or body surface area does not represent the true nature of overall organ function in the pediatric population. Therefore, understanding and integrating the role of ontogeny in designing an optimal dose (safe and efficacious) for pediatric patients is extremely important.

Allometric scaling is regularly used to predict pharmacokinetic parameters such as clearance, volume of distribution, and half-life from animals to humans (interspecies scaling) [38]. Allometric scaling can also be used to predict aforementioned pharmacokinetic parameters from adults to children and can be a very useful tool during pediatric drug development [39]. The clearance (dose/area under the curve) is the most important PK parameter because it is the inverse of exposure (area under the curve). Considering the importance of clearance, over the years, lots of efforts have been put forward to predict clearance in children from adults [40–47]. There are several methods to predict PK parameters in children such as modeling and simulation, physiologically based models, and allometric scaling. The focus of this chapter is only on allometric scaling. There are several allometric methods that can be used to predict drug clearance and are described below.

5.4 Prediction of Drug Clearance in Children

5.4.1 Allometric Scaling (Data-Dependent Exponents)

Pharmacokinetic parameters such as clearance, volume of distribution, and half-life can be allometrically extrapolated in children from adult PK parameters. One can allometrically (using equation 4.3 or 4.4) predict PK parameters in children of different ages using adult PK values especially clearance. In order to predict clearance in children, clearance is plotted against body weights (according to equation 4.3 or 4.4) of several adult subjects, and from the resulting allometric equation, one predicts the clearance of drugs in children of different age groups. This approach gives reasonably good prediction of clearance in older children (>5 years of age), but in neonates, infants, and toddlers, most of the time, the predicted clearance values can be erratic with substantial prediction error [22].

Using adult clearance data and equation 4.3, Mahmood [48] predicted the clearances of 14 drugs in children. The mean predicted clearance values were compared with the mean observed clearance values. The observed clearance values were calculated based on extensive blood sampling using compartmental or noncompartmental analysis by the respective authors of the original manuscripts. The

children were divided into two age groups (≤5 years and >5 years of age). There were 503 children (≤5 years of age), and in most of the children, the predicted drug clearance values were erratic. The prediction error of ≤30 %, ≤50 %, and ≥100 % was noted in 21 %, 33 %, and 58 % children, respectively. Out of 35 age groups, the prediction error in mean predicted clearance was ≤50 % in 18 age groups. There were 147 children (>5 years of age), and in most of the children, the mean predicted drug clearance values were close to mean observed values. The prediction error of ≤30 %, ≤50 %, and ≥100 % was noted in 63 %, 82 %, and 7 % children, respectively. Out of 15 age groups, the prediction error in mean predicted clearance was ≤50 % in 13 age groups.

5.4.2 Allometric Scaling (Fixed Exponent 0.75)

A widely used method (although incorrect) to predict drug clearance in children (from neonates to adolescents) is the use of a fixed exponent 0.75, as shown in equation 4.7.

$$\text{CL in the child} = \text{Adult CL} * \left(\text{Weight of the child} / 70\right)^{0.75} \tag{5.7}$$

where 70 kg is the standard weight of an adult.

This approach produces substantial error in the prediction of drug clearance in children ≤5 years of age, especially in neonates and infants. Mahmood [48] predicted the clearances of 14 drugs in children using equation 4.7. There were 503 children (≤5 years of age), and in most of the children, the predicted drug clearance values were erratic. The prediction error of ≤30 %, ≤50 %, and ≥100 % was noted in 14 %, 28 %, and 58 % children, respectively. Out of 35 age groups, the prediction error in mean predicted clearance was ≤50 % in 16 age groups. There were 147 children (>5 years of age), and in most of the children, the mean predicted drug clearance values were close to mean observed values. The prediction error of ≤30 %, ≤50 %, and ≥100 % was noted in 48 %, 81 %, and 6 % children, respectively. Out of 15 age groups, the prediction error in mean predicted clearance was ≤50 % in 13 age groups.

Generally, the prediction error in drug clearances in neonates and infants reached to several hundred percent from exponent 0.75 and constantly over-predicted the drug clearances in this age group. However, exponent 0.75 provided fairly accurate prediction of mean clearance of drugs in children >5 years of age. Mahmood's observation was very much in line with other investigators [49–52].

Several conclusions from "data dependent" and "fixed exponent" allometry studies can be drawn and are summarized below.

- The exponents of allometry obtained from adult data (weight vs clearance) widely varied. The variability in the exponents of allometry is the nature of allometry and there is no optimum, or reliable, or good exponent of allometry.

- In many cases, the correlation between body weight and clearance was poor, and this was mainly because the weight range of adult data in most instances was narrow. However, it should be noted that a strong correlation between body weight and clearance does not necessarily mean a good prediction of clearance in children.
- In children ≤5 years of age, in some instances, one can obtain comparable mean predicted and observed CL values of drugs, but the prediction error in individual subjects can be substantial. On the other hand, in children >5 years of age, in majority of instances, one can get a good (<50 % prediction error) prediction of mean clearance of drugs.
- Both allometric scaling and fixed exponent of 0.75 provided almost similar results and the predictive power of both approaches were erratic and unreliable in children ≤5 years of age.
- Overall, the results of these two studies indicated that prediction of drug clearance in children ≤5 years of age from adult clearance values is difficult and erratic (mean or individual), whereas for children >5 years of age, one can obtain a fairly good prediction (mean or individual) of drug clearance.

5.4.3 Boxenbaum Coefficient Method

> I have named the method after Late Dr. Harold Boxenbaum because during my many discussions with him, he emphasized on the importance of coefficients of allometry. Furthermore, through this method, I would like to pay tribute to Dr. Boxenbaum for his enormous work and contribution to allometry.

As mentioned earlier, extrapolation of clearance from adults to children <5 years of age is not simple mainly because of the lack of maturation of body organs. Considering the substantial prediction error in clearance in children ≤5 years of age based on the data-dependent allometry or fixed exponent 0.75, it is important to find a method or methods to improve the prediction of drug clearance in this age group. In allometric scaling, there is enormous focus on the exponents of allometry, but the importance of coefficients of allometry has been completely ignored. More than 30 years ago, Heusner [53] emphasized on the importance of allometric coefficients. Both the coefficients and exponents of the allometry are data dependent and will vary based on sample size, range of body weight, and the parameter of interest [54].

It was noted by Mahmood that as the body weight increases with age, the coefficient of allometry for a PK parameter may also increase (although not necessarily linearly and not always). The change in coefficient is also associated with the change in the exponents. This observation led to the adjustment of coefficient of the allometric plot obtained from adult data (body weight versus clearance).

In order to predict clearance in children, especially in neonates and infants, Mahmood [54] suggested adjusting the coefficients of the allometry. This approach termed as “Boxenbaum Coefficient Method” helped in substantial improvement in the prediction of drug clearance in the neonates and infants. The allometric model

Table 5.1 Predicted and observed clearance by Boxenbaum Coefficient Method in children from adults or adults + children

Age	Observed	Adults		Adults + children	
		Allometry	Adjusted	Allometry	Adjusted
Morphine					
Preterm	5 ± 4	101 ± 33	15 ± 5	51 ± 5	6 ± 2
Term	25 ± 22	191 ± 27	68 ± 10	109 ± 19	35 ± 6
1 week-2 months	51 ± 46	220 ± 48	89 ± 19	117 ± 31	48 ± 12
Alfentanil					
Neonates	55 ± 27	49 ± 10	27 ± 6	76 ± 12	50 ± 8
Infants	128 ± 57	87 ± 19	63 ± 14	116 ± 20	93 ± 16
Amikacin					
Neonates	6 ± 5	28 ± 4	9 ± 1	32 ± 4	11 ± 1
Infants	25 ± 17	37 ± 5	18 ± 2	42 ± 5	22 ± 3
Oxycodone					
<1 week	29 ± 21	92 ± 20	37 ± 8	75 ± 18	28 ± 7
Vancomycin					
Preterm	1.5 ± 1.2	8.2 ± 2.0	1.5 ± 0.4	11.7 ± 2.4	2.7 ± 0.6
Term	3.1 ± 2.0	14.8 ± 1.3	6.8 ± 0.6	19.4 ± 1.3	10 ± 0.8
Midazolam					
Neonates	7 ± 5	120 ± 8	72 ± 5	74 ± 7	35 ± 3

was developed from two age groups. The first group consisted only of adult data and the second group consisted of adult and children >5 years of age. The coefficients of both models were adjusted according to body weights. The results of the analysis are shown in Table 5.1 (only for few drugs and for children ≤3 months of age).

5.4.4 *Age-Dependent Exponent Model (ADE)*

A single exponent does not describe body weight versus clearance data across all age groups (neonates to adults). Similarly, a fixed exponent 0.75 cannot predict drug clearance across entire pediatric age groups [46, 49, 50, 55–57]. Mahmood proposed an age-dependent exponent (ADE) for the prediction of drug clearance in pediatrics (from neonates to adolescents).

$$\text{CL in the child} = \text{Adult CL} * \left(\text{Weight of the child} / 70\right)^{b} \tag{5.8}$$

where 70 kg is the standard weight of an adult and "*b*" is the age-dependent exponent.

The ADE model is based on four exponents for different age groups and can be used to predict clearance from neonates to adolescents from adult clearance values [46, 55–58]. The exponents as suggested by Mahmood are 1.2 for preterm neonates and 1.1 for term neonates ≤3 months old, 1.0 for >3 months to 2-year-old children,

0.9 for >2 years until 5 years, and 0.75 for children >5 years of age [57]. Different exponents used in this allometric model substantially reduced prediction error in different age groups of children compared to a fixed exponent of 0.75 across all age groups or a single estimated exponent [55–58]. The ADE model predicts mean drug clearance in children with reasonable accuracy (≤50 % prediction error) and has practical application in pediatric drug development. The prediction of drug clearance in an individual child may be erratic (prediction error >50 % was noted in 30 % of children analyzed ($n = 564$)) from the ADE model. Due to this uncertainty in the prediction of drug clearance in an individual child, ADE model should be avoided for individual prediction of drug clearance.

5.4.5 Mechanistic Versus Allometric Models

Strougo et al. [47] conducted a study to predict clearances of 18 drugs (mainly metabolized by CYP3A system) from neonates to adolescents. The clearances in children were predicted using adult clearance values using two methods: (i) allometric scaling with a maturation function and (ii) a mechanistic approach based on the well-stirred model. The allometric scaling used a fixed exponent of 0.75 on body weight and a maturation function based on CYP3A enzymatic activity. The maturation functions were evaluated by three different methods proposed by three different authors (Johnson et al. [59], Edginton et al. [60], and Lacroix et al. [61]). The mechanistic models and allometric models provided comparable results in children >3 months of age. Based on average fold error, in children <3 months of age, the performance of allometric scaling was poor than the mechanistic methods proposed by all three aforementioned methods.

Mahmood [58] reanalyzed Strougo et al. [47] data using the concept of ADE model. In Strougo et al. data, there were 28 children less than 3 months of age. Mahmood used exponent 1.2 on the body weight (irrespective of the preterm or term neonates) to predict drug clearance in children <3 months of age. There were 18 observations within twofold error (64.3 %), and only one observation was with >100 % prediction error. The average fold error was 60 %. This method provided the best result for allometric scaling compared with the methods used by three different authors. This method also provided better results than the mechanistic methods proposed by Johnson et al. and Edginton et al. This approach resulted in a much improved prediction of drug clearance in children <3 months of age.

5.4.6 Body-Weight-Dependent Allometric Exponent Model (BDE)

As mentioned earlier, a single allometric exponent does not describe the entire data across all age groups. In recent years, in population pharmacokinetic studies, a body-weight-dependent allometric exponent was incorporated [62–67]. The

concept behind this approach is that the allometric exponents are not constant over body weight or age range. The BDE model indicates that the exponents of allometry for clearance widely vary depending on body weight or age. This observation of the BDE model is a true occurrence in allometric scaling and as such the BDE model has strong scientific basis.

Generally, the exponents of allometry decrease with increasing age or body weight. For example, the exponents of allometry for morphine [63] in the BDE model ranged from 1.47 (neonates) to 0.88 (adults). Similarly, the exponents of allometry for busulphan [65] in the BDE model ranged from 1.2 (neonates) to 0.55 (adults). Body-weight-dependent exponent was also noted in a population PK study of intravenous busulfan in infants and older children by Veal et al. [68]. In this study, the age and body weight of the children ranged from 10 days to 15 years and from 3.5 to 62.5 kg, respectively. The population PK model indicated two different exponents, 1.25 for <9 kg and 0.76 for >9 kg body weight, indicating that a single exponent could not describe the data across all age groups or body weights.

5.5 Prediction of Volume of Distribution in Children

Body composition is age dependent (at least from newborn to childhood); therefore, physiologic space for drug distribution will vary until a certain age [69]. Albumin and α1-acid glycoprotein concentrations are lower in neonates and infants than older children [69, 70], as a result, free fraction of drugs increases. Increase in free fraction of a drug may also increase drug distribution in the tissues.

Volume of distribution of drugs is regularly predicted from animals to humans and generally the exponents of allometry revolve around 1.0. It has been mentioned by Mahmood [71] that exponent 1.0 can be helpful in extrapolating volume of distribution of drugs from adults to older children (>2 years of age).

In order to predict volume of distribution of the central compartment (V_c) or volume of distribution at steady state (V_{ss}) in preterm and term neonates, Mahmood [72] used the following two methods:

Method I: Three allometric exponents as described in equation 4.9 were used in this analysis:

$$V_c \text{ or } V_{ss} \text{ in the child} = \text{Adult } V_c \text{ or } V_{ss} * \left(\text{Weight of the child} / 70\right)^{1.0, 1.1, \text{or} 1.2} \quad (5.9)$$

where 70 (in kg) is the standard weight of an adult.

Method II: Besides using three fixed exponents as mentioned in method I, an allometric model from adult data was also developed (body weight vs volume of distribution). The following equation describes the model.

$$V_c \text{ or } V_{ss} \text{ in the child} = A * \left(\text{Weight of the child}\right)^{b} \quad (5.10)$$

where A is the coefficient and b is the exponent of the allometric model, respectively.

The results of the analysis can be summarized as follows:

- Exponent 1.0 is not necessarily the best exponent for the prediction of volumes of distribution in preterm and term neonates. Exponent 1.0 can produce substantial prediction error (mean values) in preterm and term neonates. Considering a wide variability in the observed volume of distribution in preterm and term neonates, Mahmood proposed to use a range of exponents (1.0–1.2). This approach provides a range of volume of distribution values which may be within the observed range of volume of distribution in preterm and term neonates.
- An allometric model (body weight vs volume of distribution) developed from adult volume of distribution values may not provide a better result in preterm and term neonates than method I. The drawbacks of the allometric model developed from adult data are small sample size, narrow weight range, and substantial physiological differences between adults and neonates.

5.6 Prediction of Elimination Half-life in Children

It has been advocated in the literature that half-life of a drug can be predicted in humans from animals by using a fixed exponent 0.25. This same exponent may be used to predict half-life in children from adults. This view, however, is not necessarily true [73]. In a study, Mahmood [73] noted that in preterm and term neonates exponent 0.25 underestimated the half-life. The predicted half-life of drugs in most of the children was erratic and unreliable. One may also predict half-life in children using relationship between clearance and volume of distribution, but this approach is also unreliable. Overall, it is difficult to predict half-life in children (from preterm neonates to older children) from adult data.

5.7 Conclusions

Allometry is a very useful tool during drug development. Interspecies pharmacokinetic allometric scaling is widely used in drug development to decide about the first-in-human dose. The principles of allometry can also be applied to intra-species scaling (adults to children). However, in order to use techniques of allometric scaling, a thorough knowledge and understanding of allometry is required.

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Chapter 6
Population Pharmacokinetics in Pediatric Drug Development

Jeremiah D. Momper, John Bradley, and Brookie M. Best

6.1 Introduction

Pediatric product development initiatives in the United States have resulted in improved product labeling, increased identification of adverse events, and development of new pediatric formulations. However, a substantial number of pediatric trials have failed to establish either safety or efficacy, leading to an inability to label the product for use in children. An important consideration is drug dosing with resulting inadequate drug exposure, which was found to be a possible contributing factor to pediatric trial failures in nearly a quarter of failed pediatric drug development programs reviewed by the US Food and Drug Administration (FDA) between 2007 and 2014 [1]. A number of scientific tools are now being applied in pediatric drug development to improve pediatric dosing and increase the success rate of pediatric trials. Population pharmacokinetics (POPPK), broadly defined as the quantitative approach to describe pharmacokinetic (PK) data and identify and characterize sources of variability in drug disposition, is one such tool that has made a significant contribution to understanding PK and drug exposure linked to clinical outcomes in the pediatric patient population. POPPK is a robust tool that can handle sparse and

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unbalanced PK data, which is common in pediatric studies secondary to the logistical and ethical considerations of studying drugs and biologics in children. Additionally, the pediatric population is highly diverse with respect to body size, renal and metabolic maturation, and hormonal status, and the population approach can be used to understand how these factors impact variability in drug disposition and response. The objective of this chapter is to provide an overview of POPPK in pediatric drug development.

6.2 Regulatory Considerations for Pediatric PK Studies

The pediatric drug development approach for regulatory approval and dosing recommendations depends upon evidence-based assumptions regarding disease progression, response to intervention, and exposure-response relationships [2]. A thorough understanding of pharmacokinetics in the pediatric population allows researchers and drug developers to make rational dosing decisions to optimize patient outcomes. The relationship between concentration and pharmacodynamic effect must be either characterized directly or extrapolated from adults. In instances where full extrapolation of efficacy is applied, such as when the disease progression, response to intervention, and exposure-response relationships are expected to be similar between adults and pediatrics, the goal of the pediatric PK study should be to sufficiently characterize PK in order to design a regimen that matches adult drug exposure in the pediatric population of interest. This approach is practically more straightforward because, as discussed by Anderson and Holford, far more research is available on pediatric pharmacokinetics than pharmacodynamics [3]. HIV infection is one therapeutic area that has used this pathway, as the effectiveness of antiretroviral drugs for HIV infection can be extrapolated from adequate and well-controlled studies in adults when supplemented with safety and pharmacokinetic studies conducted in children [4]. In many situations, a reasonable assumption can be made that exposure-response relationships will differ between adults and pediatrics. Examples include antihypertensives [5] or anti-infectives in neonates (immune-compromised, by definition) where drug exposure may need to be greater than in adults in order to achieve similar clinical outcomes. In these situations, pediatric studies should aim to characterize both the PK parameters and the PK-PD relationship to support dose selection [2]. In all cases, pediatric PK studies should be designed by taking into account all available information, such as knowledge about the drug's PK in adults, experience with products in the same class or with a similar elimination pathway, and PK studies that have been conducted in other age groups or for different indications. Meibohm et al. have reviewed the importance of prior adult data on PK parameter estimation in pediatrics and point out that priors greatly influence the fit of a pediatric POPPK model [6].

As discussed in FDA's Guidance for Industry on General Clinical Pharmacology Considerations for Pediatric Studies for Drugs and Biological Products, the two common approaches used to obtain PK information are a traditional noncompartmental analysis and a population analysis [7]. A dedicated traditional PK study with rich sampling (>8 samples) in a relatively small number of patients after a single dose or multiple doses is often conducted as the first study. Noncompartmental analysis can be used to provide preliminary estimates of PK parameters such as clearance (CL) and volume of distribution (V) for subsequent POPPK analyses. In some cases, traditional PK studies may not be necessary because of the limited value of data generated. For example, in adolescent patients (12–16 years of age), PK parameters can be reasonably estimated from adults using weight-based scaling approaches [7]. A recent study showed that for 27 drug products, prediction of drug clearance in adolescents using allometric scaling resulted in a mean absolute percentage error (MAPE) of 16.7 and 17.1 % for IV drugs and oral drugs, respectively [8]. Further, because actual adolescent clearance averaged 93.2 % of adult values for the drugs studied, the same doses are approved for the vast majority of these products [8]. Traditional PK studies may also be impractical due to blood sampling limitations in vulnerable populations like neonates. Regardless of whether initial PK parameters are obtained from prediction or a traditional noncompartmental PK study, POPPK can be applied to sparse PK samples obtained from later efficacy and/or safety studies in order to estimate population and individual means, intra- and inter-subject variability, and the impact of covariates. Data are evaluated using nonlinear mixed-effects modeling, meaning that drug or metabolite concentrations are not necessarily related to model parameters in a linear fashion.

6.3 Considerations for Pediatric POPPK Study Design and Analysis

The goal of PK studies for both adults and pediatrics is to obtain information on drug absorption, distribution, metabolism, and elimination (ADME) and to identify sources of variability in these processes. For pediatrics, important considerations include the ontogeny of drug-metabolizing enzymes and transporters, growth characteristics, genetics, and other covariates that affect drug disposition, such as liver and kidney function. These unique aspects make children physiologically different from adults and can affect the ability to predict PK based solely on adult data. For example, predictions based on scaling by body weight alone are unlikely to provide accurate predictions in the youngest children (e.g., neonates and infants) due to differences in the expression of enzymes and transporters. For example, hepatic CYP3A7 expression is higher than CYP3A4 at birth until at least 6 months of age [9]. Considerations for the design of analysis of pediatric POPPK studies are discussed below.

6.3.1 Study Design

6.3.1.1 Sample Size

Pediatric research must be conducted within the ethical framework of scientific necessity and sample size for PK studies must be derived to conform to those considerations. These pediatric subject protection requirements are driven by Subpart D of 21 CFR 50, which provides additional safeguards for children in clinical research. FDA has proposed one such approach to derive the sample size for pediatric PK studies, which prospectively targets a 95 % confidence interval within 60 and 140 % of the geometric mean estimates for clearance and volume of distribution in each pediatric age subgroup with at least 80 % power. These precision criteria, which are applicable to both noncompartmental analysis and POPPK study designs, propose a simulation-based approach to justify the sample size for pediatric studies [10]. Alternate approaches to justify the size of pediatric PK studies can be considered. In the setting of pediatric drug development, the sample size is an important topic of consideration for pediatric Written Requests under the Best Pharmaceuticals for Children Act (BPCA), such that a sponsor must enroll the specified number of patients in order to meet the terms of the Written Request and receive additional patent exclusivity.

6.3.1.2 Sampling Scheme and Innovative Sampling Approaches

The timing of sparse samples obtained in clinical trials can bias estimates of PK parameters and therefore the sampling scheme should be carefully considered in order to design studies that are as informative as possible. For example, if samples are obtained too late after a dose is given, the disposition from the first compartment can be missed. Unnecessary samples that are below the limit of quantification for the assay can also be avoided by performing preliminary simulations. Several methods to derive optimal sampling are available and will not be reviewed here [11].

Two innovating sampling approaches being utilized for the pediatric population are scavenged sampling and dried blood spots [12]. Scavenged sampling accompanied by POPPK is a relatively new approach to obtain PK data in vulnerable pediatric populations, particularly neonates. This approach measures drug concentrations in residual blood or plasma left over from samples taken for other tests within the scope of routine clinical care. As discussed by Laughon et al., scavenged sampling offers several advantages, including avoiding vascular puncture specifically for PK sampling allowing for higher rates of parental consent [13]. Potential disadvantages include drug stability problems associated with inappropriate sample storage and inaccurate recording of sample collection time. Small volumes of residual blood or plasma may also be problematic for drug assays, although the use of more sensitive analytical techniques, such as mass spectrometry, may overcome this challenge.

Recent investigations employing scavenged sampling with population pharmacokinetics have successfully characterized the PK of metronidazole [14], piperacillin [15], and fluconazole [16] in preterm infants.

Dried blood spots (DBS) have been used as an alternative to plasma or whole blood to characterize the PK of several drugs in pediatric patients [17–19]. The primary advantage of DBS in pediatric PK studies is that only micro-blood volumes are required (≤50 μL), which are collected into capillary tubes and spotted directly onto filter paper for analysis [20]. DBS-based techniques have shown accuracy and precision comparable to assays using large volumes of plasma [21]. When combined with POPPK, this approach is well-suited for pediatric populations that are traditionally difficult to study due to blood sample volume limitations, such as neonates and preterm infants. For example, a recent study reported the use of DBS to characterize the POPPK of metronidazole in preterm infants undergoing treatment or prophylaxis for necrotizing enterocolitis [18]. The derived PK model allowed for the design of specific dosage recommendations for the management of anaerobic infections associated with the disease in this population. Although the regimen requires prospective validation, this study offers valuable PK information for a drug that is commonly used in neonatal intensive care units on an empiric basis. However, as discussed by Rowland and Emmons, important considerations exist for the use of DBS in PK studies, and particular attention should be paid to the distribution kinetics of the drug of interest within whole blood [22]. For drugs with a high variability in either the fraction unbound in plasma or the blood cell-to-unbound plasma concentration ratio, caution should be exercised when using DBS as an alternative to plasma. In addition, the stability of drugs on the filter paper matrix of the DBS (including temperature-related stability), needs to be considered when assessing reliability compared with plasma sampling.

6.3.2 POPPK Analysis

6.3.2.1 Body Size

The pediatric population is extremely diverse with respect to body size. A study that includes patients across the pediatric age continuum from birth to adolescence will include a very broad range of body weights, which is in contrast to many adult studies where the weight of the smallest size individual often does not differ by more than onefold from the largest size individual. Weight can reflect the development of organ systems involved in drug disposition and therefore often exhibits a high degree of colinearity with other covariates such as indices of renal or hepatic function. The correlation between weight and other predictor variables may bias PK parameter estimates if both are included in the model simultaneously [23]. For this reason, a priori size adjustments are common for pediatric POPPK analyses prior to evaluation of secondary covariates. Size adjustments are often performed using an allometric power model where the coefficient may be either fixed (e.g., 0.75 for

clearance, one for volume of distribution) or estimated. The use of fixed exponents was derived empirically but has been supported by the relationship between physiologic variables and animal size across species. A number of readings are available for the origin, application, and limitations of the power law [24–32]. The allometric scaling approach dictates 0.75 power for clearance and a linear relationship (raised to the power of 1.0) for volume of distribution, as follows:

$$\mathrm{CL_i} = \mathrm{TVCL} \times \left(\frac{\mathrm{WT_i}}{\mathrm{StdWT}} \right)^{0.75}$$

and

$$V_\mathrm{i} = \mathrm{TVV} \times \left(\frac{\mathrm{WT_i}}{\mathrm{StdWT}} \right)$$

where $\mathrm{CL_i}$ and V_i are clearance and volume of distribution estimates in an individual, TVCL and TVV are typical values of estimates or estimates for an individual with body weight (WT) that equals the standardized weight (StdWT). Some of the reasons to include the standardized weight are the numerical stability and ease of interpretation of typical values. Using median weight or an average weight of 70 kg have both been used in modeling pediatric data.

In some cases, allometric scaling with a fixed exponent of 0.75 does not adequately describe the apparent observed relationship between clearance and body weight. For this reason, some researchers have used empirical body weight adjustment either by estimating the exponent or assuming a linear relationship between clearance and body weight. The underlying true relationship between clearance and size may possibly be dictated by allometric scaling and through the influence of a confounder, and consequently the apparent relationship does not conform to basic expectations. Some investigators have argued that allometric scaling with an estimated rather than fixed allometric coefficient more accurately predicts PK for some drugs [33, 34].

6.3.2.2 Age

In general, it is preferable to incorporate size as an initial covariate prior to evaluating additional covariates to explain variability. Age may be an important secondary covariate for pediatric POPPK analyses because it is linked to maturation of clearance pathways, such as hepatic cytochrome P450 expression or development of renal filtration and secretion. Others have argued that the requirement for age in pediatric POPPK analyses is due to the use of fixed exponents rather than direct estimation of the allometric exponent [35, 36]. For example, Wang et al. report that the scaling of propofol clearance with a fixed exponent of 0.75 is inferior to estimation of the allometric exponent [37]. The limitation of this approach is that the

effects of growth (weight) and maturation (age) on pharmacokinetic parameters cannot be separated [38]. Separation of these factors is particularly important when considering the youngest pediatric patients (neonates and infants) in whom dramatic development is taking place that cannot be accounted for by weight alone. For instance, from a pharmacokinetic point of view, a premature infant will likely be different than a full-term infant of the same body weight due to differences in the maturation of clearance pathways. Incorporation of age into the POPPK model can therefore help to optimize dosing recommendations in these circumstances. The type of model best suited to describe maturation as a function of age depends largely on how wide of an age range is included in the data. A linear model is appropriate for a narrow age range while an exponential model often better describes clearance over a wide age range (e.g., birth through adolescence) [38]. When modeling age as a potential covariate in young patients, it is also useful to separately evaluate gestational age (conception until birth), postnatal age (chronological age since birth), and postmenstrual age (gestational age plus postnatal age). When more than one of these covariates is significant for clearance or volume, a forward-addition, backward-elimination approach can be used to refine the model. For example, a recent study of fluconazole pharmacokinetics in premature infants found that postmenstrual age performed better than either gestational age or postnatal age alone as covariates for clearance [39]. It is also important to consider which age definition will be easiest to integrate into practical dosing guidelines for clinical practice. A study of ampicillin POPPK included postmenstrual age in the final PK model, although dosage recommendations were stratified by gestational age and postnatal age, similar to dosing recommendations in the past, in order to simplify dosing for clinicians [40].

The inclusion of POPPK into neonatal trials has become more pertinent since the FDA Safety and Innovation Act (FDASIA), which places emphasis on studying the neonatal population. Prior to FDASIA, less than 6 % of over 400 FDA label changes related to pediatric information involved neonates and less than 1 % of greater than 120,000 trials listed on clinicaltrials.gov involved neonates. Traditional densely sampled PK studies are virtually impossible to perform in these patients. However, POPPK is one of the tools that will allow for the successful inclusion of neonates in pediatric drug development studies.

6.3.3 Physiologically Based PK (PBPK) Modeling

Physiologically based PK (PBPK) modeling is used to build models from the basic principles of physiology and can incorporate knowledge of drug-specific parameters from in vitro studies, phase 1 adult studies, and anatomical and physiological changes in pediatric populations [41]. The complexity of these models can make it challenging to use within a population-based framework [42]. While it may be logical to attempt to use these complex model-based approaches for study design and initial dose selection, evidence has yet to be developed that these approaches are better able to predict exposures and resulting outcomes than conventional approaches

such as simulation using a POPPK model derived from adults with allometric scaling [43]. This would be particularly true in the older pediatric populations where there are fewer problems with the accuracy of allometric scaling.

6.4 Future Challenges and Application of POPPK

Prior to FDASIA in 2012, pediatric studies were usually deferred until after the approval of the adult application. This situation created a scenario where approvals for pediatric use lagged behind adult approvals by nearly a decade. FDASIA Title V stipulates that planning for pediatric studies will begin at the end of phase II, and therefore pediatric studies may now occur with less adult data to inform the trials. Early planning allows for sponsors and regulatory agencies to determine a pathway for pediatric drug development while adult studies are still underway, with the intent of faster pediatric approvals and less off-label use. Unfortunately, earlier initiation of pediatric studies poses a challenge because important decisions need to be made with limited prior adult data. Many pharmaceutical sponsors seeking drug approval in both the USA and the EU need to present a pediatric investigation plan to the European Medicines Agency even earlier, after phase I adult studies. In pediatrics, POPPK offers the ability to refine dose selection in pediatric sub-populations and provide the highest probability of successful trials.

Population pharmacokinetics has made a significant contribution to understanding PK in the pediatric patient population. POPPK has great potential for applications for the most understudied of the pediatric patients, the neonates, and for new advances in therapeutics. For this potential to be realized, POPPK in pediatric patients must rigorously adhere to the best standards of the scientific and drug development community. The sampling schemes and numbers of pediatric patients required to make precise estimates of PK parameters that then provide appropriate dosing information are critical. Regulators and drug developers must work together to ensure that POPPK is utilized appropriately to improve the success of pediatric drug development programs.

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Chapter 7
Scaling Dose-Exposure-Response from Adults to Children

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7.1 Background

For a paediatric development to be rationally informed by all available knowledge, it is necessary to systematically collect and learn from available data, expert knowledge and prior developments. Aspects such as drug formulation, bioanalytical methodology, pharmacokinetics/pharmacodynamics (PK/PD), study design and statistics should be considered when defining a development plan. In this context, model informed drug discovery and development (MID3) methodology [1] is likely to prove useful.

The extent of paediatric developments varies greatly and ranges from full developments, which parallels the contents of an adult phase II and III development, to full extrapolation of efficacy from adults to children whereby only PK and safety in children may be studied. To aid sponsors and regulators determine the required extent of development, the FDA paediatric decision tree [2, 3] proposes an algorithm to evaluate the possibilities for extrapolation of efficacy from adults to children based on disease similarity, PK/PD and PK. This framework is in line with the ICH E11 [4] and the EMA paediatric PK guideline [5] and the general approach is widely used by regulators and drug developers. However, the European regulators see the need to develop an expanded and refined quantitative framework for extrapolation [6, 7]. Extrapolation according to this concept paper can be defined as 'extending information and conclusions from studies in subgroups of the patient population (source or reference population) to make inferences for other subgroups (target population) thus reducing the need for additional studies'.

Experience in paediatric investigation plans (PIPs) [6] shows that MID3 has evolved into the tool of choice in quantifying the impact of extrinsic and intrinsic factors affecting PK and PD. Pharmacometric models can also be important tools in identifying and exploring the uncertainties that might limit extrapolation of findings from one population to the other. The use of modelling approaches in compar-

ing the course of the disease and outcomes between different paediatric developmental stages has, however, not yet reached its full potential. This chapter will highlight the value of deploying a model-informed approach to paediatric developments, and also how MID3 can improve the currently proposed extrapolation framework.

7.2 Systems Data

Every medicinal product has unique dose-exposure-response (D-E-R) characteristics. However, there are aspects related to the scaling of D-E-R from adults to children that are common across different products. For example, enzymatic maturation functions are expected to be independent of the specific drug, what would change is the fraction metabolized, if any, by the specific enzymes. This knowledge is to some extent integrated in physiological-based PK (PBPK) models, can be integrated in semi-mechanistic POP-PK models, and should be extensively referred in PIPs when discussing PK scaling from adults to children [8, 9].

At the heart of paediatric modelling approaches, there should be a systems understanding. In a pharmacological drug development setting, a system can be defined as the interplay between an organism, which could be human or other animal species, a disease and a drug. Although different drugs affect different toxicological and pharmacological pathways, the human physiology, the pathophysiology and the resulting characteristics of a disease can be identical or very similar across developments. This systems knowledge, which is lost if drugs are developed in silos, can be factored into the analysis of D-E-R, and disease relationship across populations can inform and potentially increase confidence in decision making. Systems data can inform the structure of the models, the expected variability, uncertainty and covariate effects and may eventually reduce requirements for additional clinical data to build confidence in MID3. The value of modelling systems data extends beyond product-specific extrapolation questions and can facilitate paediatric drug development as a whole.

The ultimate objective should be to reach a quantitative and systems pharmacology (QSP) understanding. QSP (adapted from the working definition in Sorger et al. 2011 [10]) is defined as the systematic approach to achieve vertical and horizontal integration of systems data through multiple measurements and modelling, with the objective to solve practical problems in drug development. Systems pharmacology data can be described as the basal biological data that describe the relevant organisms ranging from the levels of single components such as biomolecules, cells, tissues, or organ to the whole organism or a population, the pathophysiology of the disease, as well as chemical and physiochemical properties of the drug [10].

Prerequisite for such approaches would be data sharing across developments and across companies. New approaches are needed to facilitate the funding, design and conductions of studies that can fill the gaps in knowledge. Many initiatives are cur-

rently ongoing to strengthen collaborations and systems knowledge at innovative medicines initiative (IMI) and critical path institute (C-path) levels. Regulators support and are involved in discussions and evaluation of such approaches through the qualification of novel methodologies pathway.

7.3 Tools

This chapter will focus on the integration of MID3 tools, defined as empirical cross-sectional or longitudinal statistical analysis of dose exposure response, PK/PD, model based meta-analyses, semi-mechanistic PK/PD, PBPK and QSP modelling. Other statistical methods, such as Bayesian techniques and meta-analyses, are also widely used to account for prior information and to support extrapolation; however, these will not be expanded upon here.

7.4 MID3 in PIPs

MID3 has been introduced as a holistic term to describe 'a quantitative framework for prediction and extrapolation, centred on knowledge and inference generated from integrated models of compound, mechanism and disease level data, and aimed at improving the quality, efficiency and cost effectiveness of decision making' [1].

Although the concept is broadly defined, the process of MID3 is highly relevant for regulatory decision making in PIPs. MID3 is based on iterative cycles of learning and confirming which in the context of paediatric developments can be expanded as below.

7.5 Step 1 Learn

7.5.1 Collect and Evaluate Quality of the Available Relevant Data

In this first step, all relevant available data on compound, system and disease level should be collected. There is no regulatory guideline on how to collect and evaluate these data. However, the EMA points to consider on meta-analysis [11] make some valuable comments regarding the need for a clear definition of source data, approaches to maximise the quality of the data and plans for evaluation of consistency and robustness. The qualitative and quantitative distribution of data in the available datasets should be presented as the domains explored by the prior data or model and evaluated with regard to the learning objectives [12]. An example would

be that the effect of body weight on PK cannot be assessed in datasets including patients with a narrow range of bodyweights. In the world of pharmacometrics, the consistency of the bioanalytical assays and measurements is of critical importance and this should be evaluated across studies.

7.5.2 Set Modelling Assumptions and Working Hypotheses on the Differences and Similarities Between Adults and Children at Disease, PK/PD and Efficacy Level

As far as possible, modelling and simulation should be used to quantify the evidence for similarity of disease between adults and children or/and help inform a quantitative estimate of the impact of potential differences on exposure and response. The modelling process can inform the assumptions and vice versa. The D-E-R relationship in adults, if available, can inform the expectations in children and help set targets, e.g. the exposure needed for a target response. If the development is paediatric alone, no data on the adult D-E-R data will be available. However, other relevant sources of data, such as non-clinical D-E-R relationships scaled from relevant species and disease models, coupled with human system data should still be considered used to help inform the expectations for the development plan.

7.5.3 Model Evaluation

Model evaluation is an integral part of an MID3-driven approach. There are numerous approaches to model validation and, depending on the context of use, different regulatory requirements may apply [13]. In cases of models used for knowledge propagation, key assumptions that are critical for the development plan should be discussed early with the regulatory authorities, and the plan for confirming or handling the uncertainties and risks should be agreed well in time, and certainly before development in children starts. In any case, perceivable and relevant what-if scenarios should systematically be defined and simulated to evaluate the impact of the modelling assumptions and working hypotheses being violated. The integration of strategic or preferable global sensitivity analysis to explore the properties of the model is also recommended.

The plan for handling uncertainty could be addressed at a medicinal product level (i.e. PIP submissions, scientific advice) or at methodology level qualification opinion or advice. Relevant examples for qualification could be qualifying the systems data for PBPK models for an intended purpose of use, a quantitative system pharmacology model, or even more operational procedures such as novel methods for blood sampling.

7.6 Step 2 Plan

7.6.1 Assessing Impact of Uncertainties in Modelling and Assumptions, and Associated Risks

Modelling parameters, assumptions and working hypotheses always have an associated degree of uncertainty. The level of uncertainty is dependent on the extent and quality of prior knowledge and inherent to the modelling exercise. The clinical consequences should be discussed with clinical experts to define the risks to be handled. The uncertainties can partly be mitigated through the use of systems data, proper model validation and appropriate study design for addressing the open questions.

If the uncertainties and clinical risks are high, additional data would be needed to confirm assumptions. If uncertainties are high but risks are manageable, or if there are low uncertainties but high risks, additional data may be needed. The ideal scenario of manageable uncertainties and risks points to the no need of additional data.

As discussed above, the use of a MID3 approach beyond data description and simple study optimisations considered of negligible clinical risk, calls for a risk and uncertainty assessment. In addition to the standard model evaluation tools, an evaluation of the assumptions of the model and the biological plausibility is needed. In addition, a routine clinical risk assessment of the model assumptions and uncertainties will open communication pathways with clinicians and empower the method. The potential implications of a model informed decision on a development program must be weighed with regard to aspects such as the safety of the paediatric patients during trials and the ultimate probability of obtaining conclusive data. Such a process could proceed along similar lines to typical benefit risk evaluations. However, due to the quantitative nature of MID3 and the risk of the quantitative framework providing a false sense of accuracy, it is important to not lose sight of unknown unknowns.

For the MID3 framework to work, it is important to establish good communication channels between the different disciplines, i.e. clinicians, statisticians, pharmacometricians, formulation experts and pharmacologists. One of the main challenges for MID3 is to communicate assumptions and expected output to enable informed decision making on study design, dose selection, and ultimately, the possibility of extrapolation between populations. Depending on the particular clinical scenario, different levels of uncertainty may be considered acceptable. The decisions on a paediatric dose, a study design, or the rationale to extrapolate are taken once all the available options are displayed and the main assumptions are clearly weighted. Graphical displays of probable outcomes including the extreme values expected with the quantified uncertainty are valuable for decision making. The tools supporting the exercise, i.e. pharmacometrics, statistical analyses, benefit risk models, should be well described and documented for traceability and regulatory review.

7.6.2 Define Targets and Precision Criteria for the Parameters of Interest

In the MID3 quantitative framework, the process does not end with a decision on the need for further studies on PK/PD, safety and/or efficacy. It is equally important to plan for data requirements in these studies in order to confirm modelling assumptions and working hypotheses. In a classical statistical framework, this is well established through pre-specified statistical tests and sample size calculations [14]. In the MID3 framework, studies should be also sufficiently powered and optimized to meet a target precision criteria and threshold values in the parameters of interest (e.g. PK, PD or efficacy endpoints). A case-by-case approach involving discussion in a multidisciplinary team of experts is needed to define these metrics. For powering, trial simulations or other statistical methods can be used. FDA has recently proposed a standard approach for powering paediatric studies for PK assessment, which provides some practical recommendations [15].

7.7 Step 3 Confirm

The assumptions and working hypotheses will be tested and updated with the emerging paediatric data. Central to this is the comparison of model predictions with experimental data. Conclusions can be drawn on modelling assumptions regarding D-E-R and covariate effects, the appropriate paediatric dose, disease similarity and the potential for extrapolation in children. If uncertainties still persist and the risks associated with the uncertainties cannot be managed, further considerations must be given to the type and extent of data that will need to be collected to confirm the current assumptions or to test new assumptions or working hypotheses (Fig. 7.1).

7.8 Scaling Dose-Exposure-Response

The discussion on paediatric development plans often centre on the following questions: How much do the D-E-R relationships change from adults to children? And what are the clinical implications from such a change?

In order to answer these questions, an MID3 approach is needed.

The D-E-R relationship can be broken down into two different processes: dose exposure and exposure response. These will be examined separately for the purpose of the discussion; however, an integrated D-E-R analysis is recommended in paediatric developments.

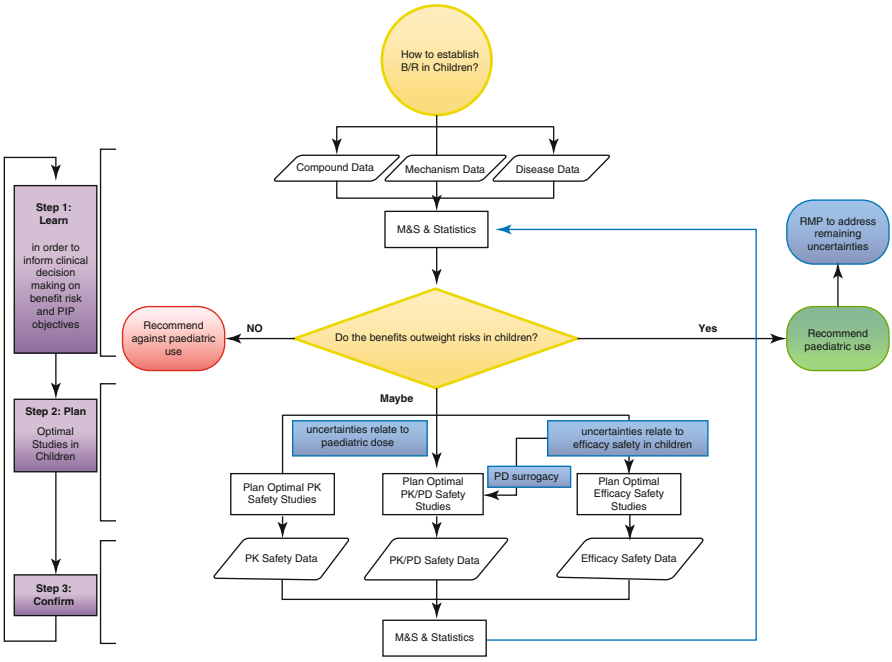

Fig. 7.1 Paediatric development planning and decision tool, including iterative loops of learning, planning and confirming

7.8.1 Dose-Exposure

In this relationship, formulation, intrinsic (e.g. maturation in metabolizing enzymes, transporters, intestinal function and organ function) and extrinsic (e.g. different food and drink effects and drug interactions) PK differences need to be understood and quantified. Although body size should be factored in as a continuous variable in the analysis of PK (i.e. using allometric scaling), maturation, food, drink and formulation effects on Liberation-Absorption-Distribution-Metabolism-Elimination (LADME [16]) may vary by developmental stage. In order to identify age-specific covariate effects, age subgroups are identified and discussed separately but should be analysed together as long as these covariate effects are captured in the analysis. The subgroup identification is also relevant for the safety analysis since organ maturation that affects PK may also impact the adverse drug reactions profile of a product. Often, but not necessarily, the assessment of PK and safety in children follows a staggered approach starting with adolescents and progressively proceeding into younger children. Depending on expected safety, PK, PD of the medicinal product and disease differences, different paediatric subsets can be defined and reconsideration of the staggered approach could be needed.

In general, the relevance of size, pubertal status, or other maturation effects on all aspects related to PK processes should be discussed. An approach that systematically addresses the LADME properties of the drug in correlation with the potential difference in the physiology of the relevant processes in the various developmental groups is encouraged. The following factors should be addressed [17–19]; however, this is not an exhaustive list and additional processes may need to be considered for a specific drug and mode of administration:

- *Liberation*: factors to account for vary with the route of administration. For orally administered drugs, factors that may differ and impact the liberation of the drug from its formulation include gastric liquid volume and pH, gastric constituents, intestinal liquid volume and pH, gastrointestinal motility and bacterial environment. Impact of maturing physiology on liberation for other routes of administration should also be considered when relevant.
- *Absorption*: factors to account for vary with the route of administration. For orally administered drugs, factors such as gastrointestinal motility, gastrointestinal blood flow, passive diffusion across enterocyte membranes, paracellular diffusion, as well as impact of maturation of intestinal and liver metabolizing enzymes and active transporters must be considered.
- *Distribution*: factors to consider include body disposition; fat, water and muscle content, protein binding, active and passive transport into organs and tissues.
- *Metabolism*: maturation of phase I and II metabolism; interplay with transporters. Efforts should be made to investigate the interaction between genetic determinism (genotype) and the influence of maturation on the functional expression (phenotype) for drug metabolism and transporters, although it is acknowledged that sparse data are available in the public domain.
- *Excretion*: organ functions, blood flows, urinary pH, maturation of transporters, bile secretion.

There is a high scientific interest in this field, and PBPK approaches, which integrate available literature as well as new data on changes in physiological maturation in children, have demonstrated ability to predict the exposure of some drugs. However, the input data for many of the physiological functions are still just rough guides and we are still learning to improve predictive PK maturational functions. Expanded and intensified research is needed to fully support the mechanistic approaches. The continued use of the methods and analysis of both the successes and failures to predict drug exposure in the relevant paediatric subsets are paramount in order to advance the field. Methods such as simultaneous modelling of several substances to describe the maturation functions and introduction of a quantitative and systems pharmacology approach could help link aspects such as sparse in vitro single organ biopsy mRNA or protein expression data and genomics to a whole body phenotypic characterization.

The peri- and postpubertal adolescent group In many instances, it can be considered similar to adults in terms of PK characteristics [5, 20]. Population PK covariate analyses in adults can support the covariate effects expected to be significant also

for the PK in postpubertal adolescents. The effect of bone maturation and rapid evolution of other physiological and psychological developments during puberty, including growth spurt, should be accounted for the peripubertal children. If peri- or postpubertal children are included in the adult phase III studies without prior confirmation of the similarity of PK, the study should be designed to provide sparse but informative PK information in this subset. A fail-safe approach, implementing measures to enable optimization of the study dose, in case of incorrect assumptions, is generally recommended. Once data in adolescents are analysed, the model should be updated to support its robustness, and predictions to explore the dose selection for the next age cohorts should be made. An approach of extrapolation of PK from adults to adolescents must be knowledge driven and requires case-by-case considerations.

The prepubertal children older than 2–3 years of age In this subset, the maturation of enzymes and transporters is expected to be largely complete, although exceptions are reported. However, size effects and other intrinsic or extrinsic factors can alter the PK in this group, especially in children younger than 6 years of age [5]. An even distribution in patient recruitment across the age range is needed in order to fully characterize PK covariates. Allometric scaling for differences in size as well as efforts to explore the impact of other influential covariates should be undertaken. Data in this subset can be used to support the robustness of the model prediction for a staggered approach and to select the doses for confirmative trials in younger children when considering the potential additional impact of maturation.

One month to 2–3 years In these children, maturation effects are expected with regard to most aspects involved in PK [5]. Aspects that need to be considered are size and maturation effects on LADME as previously described. Other intrinsic and extrinsic covariates may also differ from adults or the other paediatric subsets, such as formulation food, drink, or impact of disease on PK and efforts to explore these should be undertaken. DDIs may also have a different impact due to maturation effects.

Neonates (term and preterm) As in the 1 month to 2–3 years of age, both size and maturation effects as well as other intrinsic and extrinsic factors can be expected to impact PK [5, 21]. Due to rapid changes in size, maturation and potential variable impact of covariates induced by birth and exposure to extrinsic factors, the dose-exposure relationship is complex and difficult to predict. Limitations in the volume and number of blood samples than can safely be drawn, as well as other challenges with performing studies in preterm and term neonates call for a thorough discussion of existing knowledge and innovations in methodology to optimise sampling strategies and ensure generation of informative data. Given the difficulties in recruiting and obtaining PK samples from these children, all samples should ideally be taken at optimally informative times rather than in a random opportunistic manner.

Work Flow

The outlined stepwise strategy should be viewed as a template and adapted to the needs of the project at hand. Relevant background information about the drug should be provided to place the modelling approach in context within the drug's clinical development and provide an understanding of relevant pharmacokinetic characteristics. Focus would be on the in vitro and in vivo LADME properties of the drug and include, for example, a quantitative mass-balance diagram (Fig. 7.2) and proposed metabolic scheme with responsible enzymes and transporters. Additional information on relevant aspects such as dose and time dependencies, DDIs, pharmacogenetics or genomic information and food and formulation effects should be discussed. Every effort should be undertaken to characterise the maturational profile of the relevant processes involved in drug LADME.

This information should also help define the confidence in the paediatric MID3 scaling approach and define a plan for evaluation of sensitivity to the variability and uncertainty in the input data, model structure and underlying assumptions. Data from the older children cannot be expected to inform the maturation function in the younger cohorts, and accordingly, systems knowledge is needed in order to inform predictions of the dose-exposure relationship. Potential qualitative and quantitative changes in the contributions of the various pathways in paediatric subsets should be characterised. In some cases, it can also be relevant to consider the potential for impact of size and maturation changes during the time course of the study, i.e. for neonates or older children in studies of long duration.

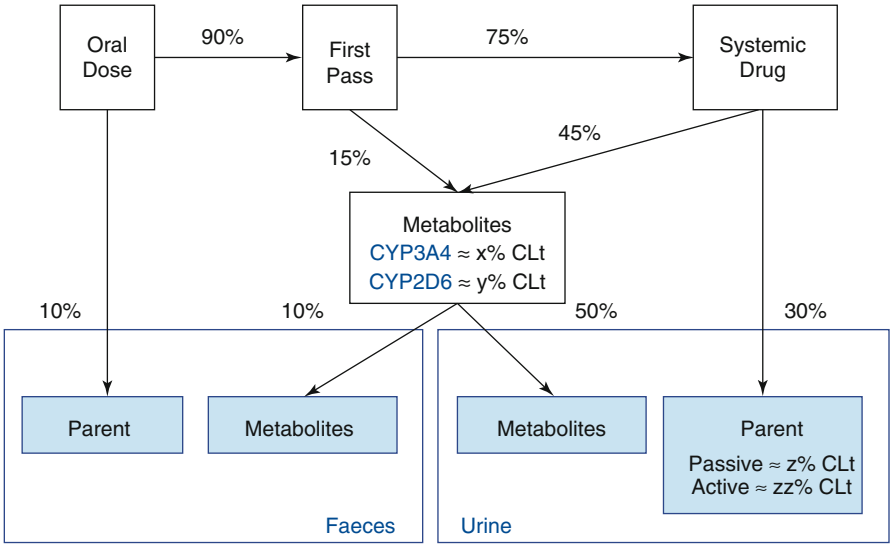

Fig. 7.2 Example of a quantitative mass-balance diagram after oral and intravenous administration of drug, showing contribution of drug absorption, first-pass drug loss and the different elimination pathways to the overall clearance of the drug [22]. The impact of transporters should also be accounted for

For the modelling approaches, it is recommended that (semi-)mechanistic models, such as PBPK or QSP models, are considered in conjunction with adult population PK modelling. For example, predictions derived from mechanistic models could be compared to a population PK adult model, sensibly scaled to the paediatric patients. It is expected that the population models can be informed by systems pharmacology knowledge. As previously described, key assumptions that are critical for the development plan should be discussed early with the regulatory authorities and the plan for confirming or handling the uncertainties should be agreed.

7.8.2 Exposure-Response

While there are plethora of studies evaluating the maturation effects on PK, the quantitative knowledge gap in PD is comparatively larger at present. Whereas principles of PK scaling often can be applied across a diverse range of compounds, maturation in a PD pathway and its clinical implications are usually specific to a therapeutic area. Few examples exist in the published domain on quantitative knowledge of maturation effects of PD. Considering the difficulties in characterizing and validating biomarkers even in adults, the characterization of a maturation effect on a PD pathway and its clinical implications is a difficult task. This calls for a joint effort and specific objectives and analyses in clinical trials to evaluate the maturation of the PD pathways. Quantitative and systems pharmacology approaches could potentially provide the framework needed to support such investigations.

In modelling exercises focused on PD, a case-by-case basis with close reference to disease area specialists is required. Characterizing the relationship between exposure and response and the potential impact of growth and maturation on this correlation is crucial for defining a paediatric dose. Both cross-sectional exposure response analyses and pharmacometric PK/PD analyses can be used. A mechanistic understanding of the disease and the mechanism of action can be included in the pharmacometric analyses, which can increase the confidence in the model (mitigate uncertainties) and, hence, in predictions from that model. During the learning phase, an understanding of E-R in adults, together with systems data may be used to generate assumptions and working hypotheses and plan the studies in children. As with PK, the most critical group where maturation in PD between adults and children are expected are neonates and toddlers (0 to 2–3 years of age). However, this could well be more variable compared to PK due to the complexity of the target(s), signalling pathways, feedback mechanisms, placebo responses as well as other intrinsic and extrinsic factors affecting the clinical manifestations and leading to difference both in the status and progression of diseases.

As in most cases, little is known on the effects of maturation and growth on PD, it is recommended to always collect PD response parameters in paediatric studies. When it comes to clinical outcomes it is not always possible to make a combined analysis of D-E-R across all paediatric subsets since the endpoints may differ in different subgroups due to feasibility or/and clinical relevance. The response parameter may also include safety endpoints or safety biomarkers. Estimating covariate

effects on the exposure-safety relationship is important and valuable to the benefit risk assessment in the paediatric population. However, safety is difficult to measure by surrogates or predict since it is often associated with both known and unknown pharmacological and toxicological mechanisms. In addition, drug-related adverse events may be related to the negative impact on growth and maturation. These types of events may be excluded only after studies in children. The safety database in children is usually expected to stand alone to support benefit risk evaluation.

Work Flow
E-R should be combined together with D-E in a D-E-R analyses. Even before initiating studies in children, D-E-R in adults should be sufficiently investigated and considered together with disease and mechanism level data to make assumptions and set working hypothesis on the expected paediatric size, maturation, covariate and disease effects on responses. Relevant background information about the drug should be provided to place the modelling approach in context within the drug's clinical development and provide an understanding of relevant pharmacodynamic characteristics of the drug. Focus would be on the pharmacodynamics properties of the drug as well as the available knowledge on the disease with regard to endpoints, disease progression, responses to placebo or similar drugs, as well as other relevant knowledge. If knowledge allows, a quantitative diagram presenting the mechanism of action and correlations with efficacy and safety should be outlined. This should summarise known and expected PK/PD or exposure-response relationships for efficacy and safety and provide information on the target concentration or exposure range based on adults or more general systems knowledge.

In general, the following aspects must be discussed and accounted for:

- Size and maturation effects as well as other intrinsic and extrinsic factors
- Baseline disease status
- Disease progression
- Placebo response
- Appropriateness of endpoints and potential relationship between differing endpoints (PD, efficacy and safety)

7.9 Conclusions

The paediatric development strategy should be defined early and should be informed by models and prior quantitative information on the system. Characterizing maturation and size effects on the D-E-R relationship is central to the paediatric investigation plan, crucial for paediatric dose selection, for informing the objectives and the design of future trials, and depending on the clinical context for extrapolation of efficacy. This can be achieved through iterative cycles of learning and confirming as described in the MID3 methodology. Systems knowledge is essential in this process at learning, planning and confirming stages.

After iterations of learning and confirming, where clinical, PK, PD are challenged in every step of the process, a more informed decision can be made in favour or against use of the medicinal product in children. This is mainly a clinical decision that needs to consider benefits, risks and associated uncertainties.

Regulators are confident that MID3 in the near future will become even more important in the planning and the analysis of paediatric clinical trials and in the decision making process. To enable the method to reach its full potential, objectives allowing MID3 analyses and learning across developments are needed in PIPs.

Disclaimer The views expressed in this chapter are the personal views of the author(s) and may not be understood or quoted as being made on behalf of or reflecting the position of the European Medicines Agency or one of its committees or working parties.

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Chapter 8
Applications of Physiologically Based Pharmacokinetic (PBPK) Models for Pediatric Populations

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8.1 Introduction

Given the difficulties for conducting clinical studies in infants and children, pediatric pharmacometrics, which applies quantitative models to account maturation of biochemical and physiological aspects of development, to predict efficacy and the likelihood of adverse reactions, is being extensively applied during pediatric drug development. More specifically, pharmacokinetics, pharmacodynamics, and disease are evaluated in different subpopulations using different methodologies. Both the European Medicines Agency (EMA) and the FDA's pharmacometrics initiative have influenced pediatric clinical design [43, 47]. Many pediatric pharmacometric examples are for drugs already on the market but used off-label in children to address the concerns on age-appropriate dose, efficacy, and safety in this special population.

PBPK modeling integrates patient/population-specific parameters related to anatomy, physiology, and pathophysiology with drug-specific properties, including physicochemical parameters, metabolic profiles, and pharmacogenomics data. PBPK modeling primarily assists in study design and predicts drug pharmacokinetic for pediatric populations. With the consideration of ontogeny for the processes rel-

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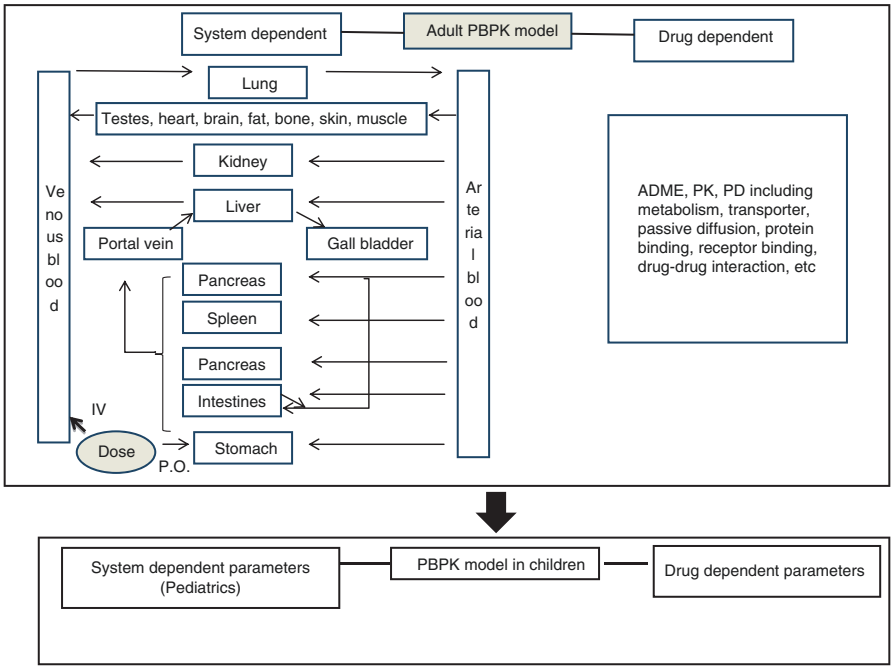

Fig. 8.1 A workflow for the development of a whole-body pediatric PBPK model

evant to drug disposition and elimination, a PBPK model may provide an option to achieve a more accurate drug-dosage prediction in various age groups of the pediatric population [4], especially for children <2 years old, including neonates [33].

To emphasize the importance of applications of PBPK in pediatric studies, 21 % of published drug PBPK models are for pediatric patients [45]. Vinks et al. [19], [20] have reviewed the published pediatric PBPK models, and Sager et al. [66] have reviewed published PBPK models for drugs including some pediatric PBPK models. These reviews covered topics such as clearance of drugs in children [46], fundamental aspects of pediatric PBPK models [4, 39], application to first-in pediatric dosing [17], kidney function in pediatrics [63], and scaling in pediatrics [67].

The common approach in developing a pediatric PBPK model is to modify an adult PBPK model, with the incorporation of the differences in growth and maturation affecting drug disposition and pharmacodynamics (Fig. 8.1). Several recent pediatric PBPK publications represented examples of applying adult PBPK models to pediatric patient populations [38, 53, 54, 61, 66, 74, 78, 86, 90].

8.2 Development of Pediatric PBPK Model

A general approach in the development of pediatric PBPK model is to modify an adult PBPK model and extend to pediatric population. Therefore, the general structure of a pediatric and an adult PBPK model has no difference and consists of both

drug-dependent parameters and physiology-dependent parameters. These parameters are used to describe the drug distribution and elimination in various compartments, which are defined by a volume, blood flow rate, and tissues. Based on purpose of interest in the application and the availability of the data, PBPK model could be a simple model assume perfusion rate limited distribution within different tissues [11, 71], or a relative complicated one considering absorption and tissue distribution with both passive diffusion process (perfusion rate limited) and active transport process (permeability rate limited) [55, 57].

Drug-specific parameters include enzyme or transporter intrinsic clearances, volume of distribution, drug solubility or formulation parameters, physicochemical parameters, plasma protein binding, membrane permeability, and tissue partition parameters. The availability of these parameters relies on in vitro assays (i.e., metabolism or transporter assays), preclinical studies, and clinical studies during the various phases of drug development. Drug-dependent parameters are independent of the system parameters.

Human system-dependent parameters (i.e., tissue volume, blood flow, organ size and weight, glomerular filtration rate, and enzyme/transporter expression) are widely available in literatures and have been summarized previously [58].

Figure 8.1 shows the structure of a typical whole-body PBPK model in which the tissues and organs of the body are arranged anatomically and connected via dynamic vascular system [4, 44]. An adult PBPK is normally developed first. The pediatric PBPK model is then developed primarily by applying age-dependent changes in physiology (system-dependent parameters). The general principles and methods in the development of pediatric PBPK model are similar as the development of an adult PBPK model. Depending on the availability of data for the studied drug, the development of a pediatric PBPK model could be followed with a bottom-up [20, 66], or a top-down [2], or a middle-out [31, 82] strategy. These strategies and principles have been extensively discussed in the above references and other literatures [57].

In contrast to the development of adult PBPK model, developmental changes (maturation trajectories) affecting drug absorption, distribution, metabolism, and elimination (ADME) have to be addressed and specified in order to develop a pediatric PBPK model. Some of the physiology parameters in PBPK models with age-dependent developmental changes are important factors contributing to the exposure differences between adults and children. These include (a) anatomical differences (e.g., change in blood volume, organ size, body fat, plasma protein binding), (b) changes in hepatic metabolism (enzyme ontogeny) or transporter ontogeny, and (c) organ maturation (e.g., renal maturation).

8.2.1 Age-Dependent Physiology

One of the examples for the workflow shown in Fig. 8.1 is the PBPK model developed for theophylline and midazolam in infants, children, and adults [5]. A whole-body PBPK model considering various tissues including brain, heart, lung, liver, kidney, skin, stomach, gut, pooled spleen with pancreas, muscle, fat carcass, and blood were developed. Age-dependent body weights and tissue volumes were

adapted from literature values on infants and children, while blood flows were scaled from adults based on cardiac output, with the exception of liver blood flow in children (QL_{child}, *L*/min). Pediatric liver blood flow was adjusted from adult values (QL_{adult}) by the ratio of body surface area (BSA, m^2) of children vs. adults.

$$QL_{child} = \left(BSA_{child} / BSA_{adult}\right) \times QL_{adult} \tag{8.1}$$

BSA for children could be estimated using the equations of Dubois and Dubois [16] (Eq. 8.2) or Haycock et al. [24] (Eq. 8.3). Brion et al. evaluated different equations for the estimation of BSA in newborn infants and recommended to use the Dubois and Dubois equation for BSA in children weighing >15 kg, and the Haycock equation for BSA in children weighing ≤15 kg [7].

$$BSA\left(m^2\right) = \left(W^{0.425} \times H^{0.725}\right) \times 0.007184 \left[16\right] \tag{8.2}$$

$$BSA = 0.024265 \times W^{0.5378} \times H^{0.3964} \left[7\right] \tag{8.3}$$

(*W* is mass in kg, and *H* is height in cm)

Plasma protein binding can also be modified by age-related changes in serum albumin (Alb) concentrations and α1-acid glycoprotein (α1AG) concentrations. Among various models fitted to plasma protein concentration as a function of age (in days), Eqs. 8.4 and 8.5 were found to be the most relevant for use with Alb and α1AG, respectively [41, 49, 51, 83, 87].

$$\begin{gathered} Alb\left(g/L\right) = 1.1287 \times \ln\left(Age^{*}\right) + 33.746 \\ {}^{*}\text{days, value truncated at } 10,000 \text{ days} \end{gathered} \tag{8.4}$$

$$\alpha 1AG\left(g/L\right) = \frac{0.887 \times Age^{0.38}}{8.89^{0.38} + Age^{0.38}} \tag{8.5}$$

Changes in the unbound fraction (fu) of drugs in pediatric subjects ($fu_{Pediatric}$) can be estimated using Eq. 8.6 [49].

$$fu_{Pediatric} = \frac{1}{1 + \frac{\left(1 - fu_{Adult}\right) \times [P]_{Pediatric}}{[P]_{Adult} \times fu_{Adult}}} \tag{8.6}$$

(fu_{Adult} and $fu_{Pediatric}$ are the average unbound fraction of drug in healthy adults and pediatric populations, respectively)

[P] is the plasma protein concentration (mol/L); and $[P]_{pediatric}$ and $[P]_{Adult}$ are plasma protein concentration for pediatric and adult, respectively.

Information on changes in small intestine length, diameter with age, gastric empty time, and gastric pH used in PBPK models are often derived from the Reference Man report of the International Commission on Radiological Protection

[28]. Based on data from ICRP, Johnson et al. [32] developed linear equations for intestinal length and diameter both related to BSA, respectively (Eqs. 8.7 and 8.8).

$$\text{Intestinal length}\left(\text{m}\right)=2.56\times\text{BSA}+2.95 \tag{8.7}$$

$$\text{Intestinal diameter}\left(\text{m}\right)=0.016\times\text{BSA}+0.0159 \tag{8.8}$$

The difference in gastric pH and gastric emptying time between adult and children are summarized by Yu and Zheng et al. [89]. However, further studies are needed to evaluate the contradictory information found from different studies [37, 50].

Liver is an important organ for many drugs because of the hepatic metabolism. Johnson et al. [32] conducted a meta-analysis to study the changes in liver volume from birth to adulthood and created (Eq. 8.9) to predict the liver size changes based on BSA [34].

$$\text{Liver volume}\left(L\right)=0.722\times\text{BSA}^{1.176} \tag{8.9}$$

8.2.2 *Ontogeny of Hepatic Cytochrome P450s (CYPs) and Drug Transporters*

For compounds with extensive hepatic metabolism, it does not only needs to consider the changes in liver size or volume as well as the ontogeny in transporters and enzymes need to be considered. Ontogeny of individual cytochrome P450s (CYPs), after the measurements of enzyme expression and activity, has been evaluated in many studies [15, 29, 32]. Hyperbolic functions describing the development of some CYP enzymes have been summarized by Johnson et al. [31] (Table 8.1). With the introduction of enzyme ontogeny and other age-dependent physiological changes, several pediatric PBPK models have been successfully developed to predict the exposure of drugs that undergo hepatic metabolism [52, 88].

Nong et al. [52] developed an age-dependent (birth to adult) PBPK model for the solvent toluene, using the ontogeny of CYP2E1 hepatic metabolism. Nong et al. relied on CYP2E1 activity from 116 autopsy samples reported by Johnsrud et al. [35] for newborns to adults. The remaining age-dependent tissue volumes, blood flows, and ventilation rates were computed for each age based upon the equations of Price et al. [60] and Haddad et al. [23]. The intrinsic clearance of toluene for each child ($CL_{\text{int-child}}$, L/h) was calculated from the measured hepatic CY2E1 protein content (pmol CYP2E1/mg protein) and the volume of liver ($V_{\text{liver-child}}$, L) by

$$\text{CL}_{\text{int}-\text{child}}=\left(\frac{\text{CL}_{\text{int}-\text{adult}}}{\left[\text{CYP2E1}\right]_{\text{adult}}\times V_{\text{liver}-\text{adult}}}\right)\times\left[\text{CYP2E1}\right]_{\text{child}}\times V_{\text{liver}-\text{child}} \tag{8.10}$$

Table 8.1 Data used to generate hyperbolic functions describing the development of individual cytochrome P450 (CYP)

Enzyme	Location	Fractional expression at birth relative to adult	Time to half adult expression	Hyperbolic function (fraction of adult CYP abundance)	r^2	Reference
CYP1A2	Hepatic	Negligible	0.9	$\frac{1\times \text{Age}^{1.41}}{1.13+\text{Age}^{1.41}}$	0.99	[14, 70, 74]
CYP2B6	Hepatic	Negligible; insufficient data	1.31	$\frac{1.07\times \text{Age}}{1.31+\text{Age}}$	0.99	[74][a]
CYP2C8	Hepatic	0.3	0.02	$\frac{0.716\times \text{Age}}{0.02+\text{Age}}+0.3$	0.89	[38, 74, 77]
CYP2C9	Hepatic	0.21	0.01	$\frac{0.821\times \text{Age}}{0.01+\text{Age}}+0.21$	0.91	[38, 74, 77]
CYP2C18/19	Hepatic	0.23	0.99	$\frac{0.857\times \text{Age}}{0.99+\text{Age}}+0.23$	0.87	[38, 74, 77][b]
CYP2D6	Hepatic	0.036	0.101	$\frac{1.01\times \text{Age}}{0.101+\text{Age}}+0.036$	0.99	[78]
CYP2E1	Hepatic	Negligible	2	$\frac{4.22\times \text{Age}^{0.27}}{7.66+\text{Age}^{0.27}}$	0.99	[33, 81]
CYP3A4/5	Hepatic	Negligible	0.31	$\frac{1\times \text{Age}^{0.83}}{0.31+\text{Age}^{0.83}}$	0.97	[40, 73, 76]
CYP3A	Gut	0.42	2.36	$\frac{0.639\times \text{Age}}{2.36+\text{Age}}+0.42$	0.98	[31]

Johnson et al. [30]

[a]Japanese subjects; Caucasians assumed to be similar

[b]Data for CYP2C19 only; CYP2C18 assumed to be similar

r^2 correlation coefficient

The hepatic clearance (CL_h, *L*/h) for each child was then calculated by

$$CL_h = \left(\frac{CL_{int} \times QL}{CL_{int} + QL} \right) \tag{8.11}$$

where QL (*L*/h) is the liver blood flow.

The variability for area under the curve (AUC) calculations for the children was within a factor of 2, and the 95th percentile AUC value for the low metabolizing neonatal group was greater than the mean adult AUC by a factor of 3.9. Nong et al. demonstrated that simply scaling metabolism by a surface area correction underpredicted AUC values determined with child-specific data on CYP2E1 content for infants under 1 year of age and neonates.

In addition to CYPs, drug transporters, which are expressed throughout the body and important for drug ADME, also display ontogeny [30]. However, compared to the relatively abundant ontogeny data available for metabolizing enzymes, information regarding transporter-mediated drug disposition in terms of tissue-specific transporter abundance and ontogeny of specific transporter systems is currently limited [72]. It is difficult to conduct transporter studies to directly evaluate the transporter ontogeny in vitro, because of the difficult access to fresh hepatic tissue in infant population. Studying transporter expression in liver samples of pediatric patients at different stages of hepatic disease provide some information on chronological changes of transporters in different disease stages [10]. It was found that, at early-stage of cholestasis, most canalicular transporters and sinusoidal uptake transporters, including bile salt export pump (BSEP, ABCB11), multidrug-resistant protein 3 (MDR3, ABCB4), multidrug-resistant associated protein 2 (MRP2, ABCC2), sodium-dependent taurocholate cotransporting polypeptide (NTCP, SLC10A1), organic anion transporter (OATP, SLCO1A2), were downregulated. At late-stage cholestasis, BSEP levels returned to normal, while efflux transporters MDR3 and MDR1 (ABCB1) were upregulated, and MRP-2 was downregulated. Other sinusoidal efflux transporters, such as organic solute transporter alpha/beta (OSTalpha/beta) and MRP4, were also upregulated [10]. However, how the information on relative transporter activity obtained from disease state is interpreted to obtain transporter ontogeny and applied to other pediatric populations (whether healthy or other disease populations) needs to be further evaluated.

Future studies are needed to understand transporter ontogeny; in able to scale of adult models utilizing transporter-mediated processes toward pediatrics. Nevertheless, if sufficient information is available, relative transporter activity expressed in the form of transporter intrinsic clearance (CL_{int}) may be scaled from adults toward pediatrics using age-dependent protein concentration or activity levels [45].

8.2.3 Renal Function

Changes in the renal clearance of drugs are other factors to be considered in the development of pediatric PBPK models. Nephrogenesis begins at 9 weeks of gestation and is completed by 36 weeks of gestation, when there are around 1,000,000 nephrons in each kidney [3]. The kidneys are anatomically and functionally immature at birth. The clearance maturation of drugs that are extensively cleared by renal elimination is normally reflected by the maturation of glomerular filtration rate (GFR) or creatinine clearance (CrCl).

Equations used frequently to estimate renal function in pediatric populations include modified Shwartz equations [8, 68, 69] (Eq. 8.12) and the Cockcroft-Gault equation (Eq. 8.13), as described in *FDA Guidance for Industry*: *General clinical pharmacology considerations for pediatric studies for drugs and biologic products*.

Modified Schwartz equation (*pediatric patients <12 years of age*): Eq. 8.12

$$\mathrm{CrCl}\left(\mathrm{ml/min/1.73m^2}\right) = \left(K \times \mathrm{Ht}\right) / \mathrm{Scr} \tag{8.12}$$

height (Ht) in cm; serum creatinine (Scr) in mg/dl
K (proportionality constant):

Infant (LBW <1 year): $K = 0.33$
Infant (Term <1 year): $K = 0.45$
Female Child (<12 years): $K = 0\ .55$
Male Child (<12 years): $K = 0.70$

Cockcroft-Gault equation (*pediatric patients ≥12 years of age*): Eq. 8.13

$$\begin{aligned}\mathrm{ClCr}\left(\mathrm{ml/min}\right) = &\left[\left(140 - \mathrm{age}\right) \times \mathrm{weight\ \ in\ \ kg}\right] \\ &/\left[\mathrm{Scr} \times 72\right]\left(\times 0.85\ \ \mathrm{if\ \ female}\right)\end{aligned} \tag{8.13}$$

Johnson et al. also developed an equation for GFR [32] (Eq. 8.14) to describe renal function up to 20 years of age against an independent dataset [65].

$$\mathrm{GFR}\left(\mathrm{ml/min}\right) = \left(-6.1604 \times \mathrm{BSA}^2\right) + \left(99.054 \times \mathrm{BSA}\right) - 17.74 \tag{8.14}$$

Due to the rapid developmental changes of physiological factors affecting the PK of drugs in newborns, the PK of drugs could differ significantly among preterm (especially extremely low birth weight), term neonates, and infants. Therefore, extra consideration in addressing the difference in organ maturation and ontogeny in newborns and preterm neonates is needed to make better decision in dose selection for these particular populations. Claassen et al. developed a PBPK preterm neonate model after a comprehensive literature search on physiological information of preterm neonates [12]. In order to predict appropriately the age-dependent GFR in the preterm population, Claassen et al. modified Rhodin's equation [60] and introduced a small fractional

offset in the GFR (fGFR$_{premat}$) to correct for a tendency to underestimate slightly the observed median GFR in preterm below 32 weeks of gestation (Eq. 8.15).

$$\mathrm{GFR} = \left\{ \left(\frac{\mathrm{PMA}^{\mathrm{Hill}}}{\mathrm{TM50}^{\mathrm{Hill}} + \mathrm{PMA}^{\mathrm{Hill}}} \right) \times \left(1 - f\mathrm{GFR}_{\mathrm{premat}}\right) + f\mathrm{GFR}_{\mathrm{premat}} \right\} \times \left(\frac{\mathrm{Volume}_{.\mathrm{kideny}}}{440\mathrm{mL}} \right) \times \mathrm{GFR}_{\mathrm{mat}} \tag{8.15}$$

(PMA: Postmenstrual age; Volume.$_{kidney}$: volume of kidney; fGFR$_{premat}$: a small fractional offset in the GFR of preterm neonates; GFR$_{mat}$: GFR of term neonates)

After incorporation of the factors including adjusted renal maturation and liver maturation (including hepatic enzyme ontogeny) into the preterm PBPK model, the authors evaluated the performance of their model with two drugs: amikacin and paracetamol (acetaminophen) [12]. The predicted plasma concentration-time profiles of the two drugs were compared to the observed in vivo data and appropriately simulated the concentrations for a large range of gestational and postnatal ages including preterm neonates.

8.3 Evaluation and Validation of Pediatric PBPK Model

After the development of adult PBPK model with the input of drug-dependent and system-dependent parameters, a pediatric PBPK model could be developed based on modifications on the adult PBPK model by extending to pediatric population and considering above developmental changes.

Before modifying an adult PBPK model to a pediatric PBPK model as shown in Fig. 8.1, the adult PBPK model has to be well validated. However, there is no consistent agreement on standards and criteria to determine the quality of a PBPK model [70]. Generally, it is recommended a prior criterion (e.g., a common twofold criterion) should be predefined before model development to determine the model performance. A generally accepted good practice in assessing the quality of PBPK model is to apply an independent in vivo dataset that was not used in the model development process and in situations where one of the parameters is altered, such as dataset from a drug-drug interaction (DDI) or a special population (e.g., renal or hepatic impaired populations, alternative genotype population) [36, 48, 91]. The adult PBPK model should be able to adequately describe the PK or time-concentration profiles after i.v. or oral administrations against observed in vivo data by meeting the predefined criterion.

After extending the adult PBPK model to develop the pediatric PBPK, it could be evaluated similarly as described above for adult PBPK model. However, one challenge in the pediatric model evaluation is that there is generally sparse pediatric clinical data available for verification. Furthermore, a smaller sample size was used

in some of the pediatric clinics, which might bring in a larger trial-to-trial variability because of some extreme subjects in the trial. This might lead to a situation that model fits well against one dataset but fits poorly against another clinical observation for the same drug [1].

Application of PBPK modeling to support various aspects of pediatric research and development is highly attractive and of continuing interest. The following are some additional examples not referenced above.

8.4 Examples of the Successful Application of PBPK Models in Pediatrics

Ginsberg et al. [22] created a PBPK model for caffeine and its metabolite, theophylline. The compartments for the model included liver, kidney, fat, and well-perfused and slowly perfused tissues. Caffeine and theophylline are cleared via metabolism by CYP1A2 as well by other CYP isoforms and excreted in urine. Since neonates are administered caffeine, the age-dependent pharmacokinetics of these compounds is of interest and how it compares to adults. At very young ages, when CYP1A2 is immature [49], renal clearance is the prevailing elimination process. However, the systemic clearance rates for these drugs were still less in neonates than in adults. Ginsberg et al. scaled in vivo clearance through hepatic metabolism data of caffeine and theophylline to predict adult and age-dependent metabolism. To explain the data, a secondary metabolic pathway was proposed for conversion of theophylline to caffeine, and this proposed pathway was only active in neonates. With the consideration of metabolism pathways switch, the pharmacokinetics of caffeine and theophylline could be predicted in neonates.

Yang et al. [88] developed and validated an adult PBPK model for methadone, and then scaled appropriately to simulate PK in children aged 0–24 months. Methadone is a lipophilic mixture of R and S enantiomers. Each enantiomer has different affinities toward P450 enzyme isoforms, with the CYP3A family of enzymes dominating. Methadone's pharmacokinetics is also influenced by plasma protein binding (α1-acid glycoprotein and albumin), body fat, and urinary clearance. Yang et al. constructed an age-dependent PBPK model using equations of organ volumes, blood flows, plasma protein concentrations, and hepatic P450 enzyme activities based on measured variability in CYP3A enzyme expression levels. Yang et al. suggested that dosing schedules required individual information through drug monitoring to achieve targeted therapeutic serum levels. The simulations in pediatric populations showed that when doses were designed for individuals based on prior enzyme expression information, inter-individual variability in methadone kinetics could be greatly reduced.

Vogt [85] used a pediatric PBPK population model for dosing of milrinone in pediatric populations, which is a drug used for treatment and prevention of low cardiac output syndrome after open-heart surgery. The model accounted for drug-related changes increases in cardiac index and associated increased blood flows to

compartment, impaired kidney function (GFR, using KIM-1 as a biomarker) and altered phase II conjugation (UGT1A6) rates for the drug. The in vivo exposure of milrinone was predicted by this model for adults with or without open-heart surgery, pediatric patients with open-heart surgery, as well as adults and pediatric patients with and without low cardiac output syndrome. The average fold error in predicting the pharmacokinetics of milrinone was 1.5. The author stated that current milrinone doses for cardiac output syndrome were not optimal for the therapeutic targeted peak and trough range; thus, PBPK modeling can assist in dose selection of milrinone, while conventional PKPD models do little help.

Hsien et al. developed a PBPK model for sildenafil to predict age-specific doses [25]. An adult PBPK model for sildenafil was developed and validated. Then, an age-modified PBPK model was used to predict plasma time-concentrations of sildenafil in children at different age groups after the administration of a weight-normalized dose. The simulations showed that in pediatric populations 3 months or older, the exposure of the same weight-normalized dose increased as the age of children increased. Therefore, it is necessary to adapt age-specific dose to achieve a relatively constant drug exposure in children and adults, which is 0.8 mg/kg for 3 months to 4 years; 0.5 mg/kg for children between 5 and 8 years old; and 0.35 mg/kg for children older than 8 year old, as well as in adults. Due to the limited pediatric sildenafil PK data, the above simulations of sildenafil have not been validated with clinical data; nonetheless, the modeling exercise will potentially save time and effort, and reduce the number of pediatric trials.

A further extension of PBPK models is to include a pharmacodynamic (PD) component to predict drug exposure-response relationships in PBPK-PD models. By integrating age-dependent changes in the factors, as summarized above, that affect drug pharmacokinetics, PBPK-PD models can quantitatively characterize drug target-site distribution, drug target binding and activation, and transduction mechanisms. Most importantly, if incorporating disease population parameters into the model, PBPK-PD models can also characterize the interaction of drug effect with disease processes [13].

Some PBPK-PD models have been applied for pediatric studies [6, 9]. Edginton et al. developed a PBPK-PD model of propofol to predict its PK and PD in various patients groups, including children, pregnant women, young men, normal-weight adults, and obese adults [18], and compared the predictions to those obtained with regular compartment models. They found that PBPK-PD model provided increased flexibility over compartmental models, with better predictions of both PD endpoints: loss of consciousness and recovery of consciousness.

8.5 Summary

Since the publication of Best Pharmaceuticals in Children Act (BPCA) and Pediatric Research Equity Act (PREA), it has been increasingly evident that adult safety profiles cannot be extended directly to children, even when the disease process are the

same [75]. Therefore, pharmacokinetic modeling, including PBPK models, has been extensively applied to assist pediatric studies. PBPK modeling has been initially developed to assess the risk of exposure to toxic chemicals and predict the organ-specific toxicity [56]. With the further understanding of human physiological developments in adults and children, PBPK modeling has been extensively applied in the areas of drug-drug interactions, dose selection, clinical trials design, and formulation development [25, 26]. PBPK potentially offers a great platform to meet the currents needs of pediatric drug development and registration.

Some workflow practices for common pediatric PBPK applications, similar as the one shown in Fig. 8.1, have been summarized in other publications [4, 67]. Individual PBPK models can require a considerable effort to build. PBPK modeling for pediatric dose selection requires knowledge of drug properties (e.g., physicochemical data, clearance), scaling to pediatric physiology (e.g., organ size, blood flow), and accommodation for age-dependent organ maturation and enzyme/transporter ontogeny. The refinement and validation of these models require available actual organ/tissue bio-distribution and pharmacokinetic data in adults and experimental animals, PK data after i.v. administration are preferred to avoid any confounding with absorption-related process, which is another area relatively unknown in children. The necessary adult PK/PD data, as well as correct parameterization of drug-dependent and system-dependent parameters, are needed to accurately predict drug exposure in pediatric populations. Further studies are needed to understand the rapid physiological changes in pediatric populations, especially newborn/preterm infants, to have a better prediction in these special populations.

PBPK modeling holds considerable promise for predicting drug exposures in pediatric populations, especially in the youngest population. However, the advantage of PBPK models over other pharmacokinetic models in the development of new therapeutic drugs needs to be further evaluated with more case studies. Given the interest in modeling and simulation for drug development in pediatric patients and the fulfillment of the requirements of BPCA and PREA, the proper place of PBPK modeling in pediatrics should be determined in the next decade.

A workflow for the development of a typical whole-body pediatric PBPK model was described, in which the tissues and organs of the body are arranged anatomically and connected via dynamic vascular system [4, 44]. An adult PBPK is normally developed first. The pediatric PBPK model is then developed primarily by applying age-dependent changes in physiology (system-dependent parameters) with consideration on organ maturation, and ontogeny.

Disclaimer The opinions in this paper do not necessarily reflect the official views of the FDA.

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Chapter 9
Perinatal Pharmacology and Maternal/Fetal Dosing

Iftekhar Mahmood, Gilbert J. Burckart, and Robert M. Ward

9.1 Introduction

One of the last frontiers in pediatric studies is those studies directed at the care of the maternal-placental-fetal unit. Because of the concern for teratogenicity and the possibility of harm to the mother or the fetus, drug development studies have largely avoided any study in pregnant women. However, this has been a major inhibition to obtaining important scientific and clinical information that would allow better care of the mother, the fetus, or the maternal-placental-fetal unit.

This chapter will cover the important regulatory requirements that pertain to maternal and fetal studies, discuss clinical pharmacology concerns, and give examples of drug development programs that would benefit from a structured clinical pharmacology assessment of drug therapy for the maternal-placental-fetal unit.

9.2 Regulatory Considerations

The thalidomide tragedy of the 1950s and early 1960s may have precipitated the Kefauver-Harris Amendments to the Food Drug and Cosmetic Act that brought about the need for efficacy studies as well as safety studies, but it also had an adverse effect

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on the inclusion of potentially pregnant women in drug development studies. In 1977, the FDA issued a guideline titled "General Considerations for the Clinical Evaluation of Drugs" that specifically prohibited the inclusion of women of childbearing potential from inclusion in early drug development programs [1].

In July 1988, the FDA's "Guideline for the format and content of the clinical and statistical sections of an application" specified the need to identify the sex of subjects in the Clinical Pharmacology section of an application [2]. In response to this concern, in 1990, the NIH formed the Office of Research on Women's Health (ORWH). In 1993, the FDA specifically withdrew its prohibition on the inclusion of women of childbearing potential from early phase studies through its "Guideline for the Study and Evaluation of Gender Differences in the Clinical Evaluation of Drugs." Finally, the FDA's Office of Women's Health was established in 1994 by a congressional mandate.

Under the Food and Drug Administration Modernization Act of 1997 (FDAMA), Sec. 115 Clinical Investigations. (b) Women and Minorities. – Section 505(b) (1) 21 U.S.C. 355(b) (1) was amended by adding at the end the following: "The Secretary shall, in consultation with the Director of the National Institutes of Health and with representatives of the drug manufacturing industry, review and develop guidance, as appropriate, on the inclusion of women and minorities in clinical trials…" [3]. Consequently, females currently comprise 49 % of subjects in HHS-funded studies that include both male and female participants, but studies of the maternal-placental-fetal unit are still lacking.

While current FDA regulations pertaining to informed consent and institutional review board review would still pertain to pregnant women, the fetus is not covered under the current pediatric legislation (BPCA and PREA [4]) covered in other chapters of this book. The FDA does not have regulations pertaining to fetal research. However, the Department of Health and Human Services (HHS) does have 45 CFR 46 Subpart B which pertains to pregnant women, fetuses, and neonates.

45 CFR 46 Subpart B took effect on December 13, 2001. This section applies to all HHS conducted or supported research involving pregnant women, human fetuses, neonates of uncertain viability, or nonviable neonates, unless exempt. Part B establishes the conditions which have to be met for the inclusion of pregnant women and fetuses. Where scientifically appropriate, preclinical studies, including studies on pregnant animals, and clinical studies, including studies on nonpregnant women, have to have been conducted and provided data for assessing potential risks to pregnant women and fetuses. Any risk has to be the least possible for achieving the research objectives.

Under Subpart B, the risk to the fetus is that caused solely by interventions or procedures that hold out the prospect of direct benefit for the woman or the fetus, or if there is no such prospect of benefit, the risk to the fetus is not greater than minimal and the purpose of the research is development of important biomedical knowledge which cannot be obtained by any other means. This introduces the concept of minimal risk to the fetus.

Minimal risk means that the magnitude and probability of harm or discomfort anticipated in the research are not greater in and of themselves than those ordi-

narily encountered in *daily life* or during the performance of routine physical or psychological examinations or tests. Obviously, the concept of minimal risk is open to interpretation, and institutional review boards (IRBs) are responsible for that interpretation. In a study by Shah et al. [5], 18 % of IRBs considered that a blood draw was more than minimal risk in children, and 6 % of IRBs considered lumbar puncture without sedation to be minimal risk. Therefore, the interpretation of minimal risk for the fetus will have to conform to the potentially broad range of interpretations of local IRBs.

Informed consent for studies involving the fetus is also complicated in regard to the participation of the father of the fetus. In this case, Subpart B is specific (46.204). Acceptable levels of risk and the consent are indexed to the prospect of direct benefit to the mother and the fetus. If the research holds out the prospect of a direct benefit both to the pregnant woman and fetus, this research requires informed consent of the pregnant woman but does not require informed consent of the father. If the research holds out the prospect of a direct benefit to the pregnant woman, this research requires informed consent of the pregnant woman but again does not require informed consent of the father. In a study in which the research holds out no prospect of benefit for the woman nor fetus and risk to the fetus is not greater than minimal and purpose of research is development of important biomedical knowledge that cannot be obtained by other means, then this research requires informed consent of the pregnant woman but does not require informed consent of the father. Paternal as well as maternal consent will be required if the research is intended to benefit solely the fetus, unless the father is unable to consent due to unavailability, incompetence, temporary incapacity, or the pregnancy resulted from rape or incest.

If the IRB does not approve the study, Subpart B does provide a chance for the study to proceed. Subpart B permits the HHS Secretary to conduct or support research that the IRB does not believe meets the requirements of subpart B, if the secretary finds that the research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of pregnant women, fetuses, or neonates. The HHS Secretary must first consult with experts in pertinent disciplines and provide for public comment and review, including a public meeting announced in the Federal Register.

Subsequently, a number of FDA Guidances have been developed that pertain to the mother and fetus. Some of these guidances include:

- Guidance for Industry: M3 (R2) Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals (February, 2013) [6]
- Reviewer Guidance: Evaluating the Risks of Drug Exposure in Human Pregnancies (April, 2005) [7]
- Guidance for Industry: Establishing Pregnancy Exposure Registries (August, 2002) [8]

- Guidance for Industry: Considerations for Developmental Toxicity Studies for Preventive and Therapeutic Vaccines for Infectious Disease Indications (February, 2006) [9]
- Guidance for Industry: Pregnancy: Lactation and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products—Content and Format (June, 2015) [10]
- Guidance for Industry: Pharmacokinetics in Pregnancy—Study Design, Data Analysis, and Impact on Dosing and Labeling (October, 2004) [11]

The International Conference on Harmonization (ICH) has also developed a Guidance on the in vitro testing of drugs for reproductive toxicity [12]. This Guidance calls for general toxicology studies in two species, and histopathology of female reproductive organs. It also has sections that deal with fertility and early embryonic development to implantation, effects on embryo-fetal development (teratogenicity), and prenatal and postnatal development including maternal function.

One of the more important guidances for a clinical pharmacologist working with pregnant women is the Guidance on Pharmacokinetics in Pregnancy—Study Design, Data Analysis, and Impact on Dosing and Labeling. URL govt doc. (http://www.fda.gov/downloads/Drugs/.../Guidances/ucm072133.pdf). This Guidance includes topics such as deciding whether to conduct a pharmacokinetic study in pregnant women, study design considerations such as whether to use a longitudinal design or a population PK design, and other important design considerations such as sample size. This Guidance also covers data analysis and labeling related to the pregnant woman.

Consideration of the impact on the fetus is becoming more prevalent in pediatric drug development. For example, the term "fetal" can be found in the medical and clinical pharmacology reviews of 29 of the 213 (14%) products with pediatric studies submitted under FDA Amendments Act of 2007 (FDAAA) and the FDA Safety and Innovation Act of 2012 (FDASIA). These references relate to fetal toxicity, where multiple examples can be found, both as a result of animal studies and human observations; establishment of a pregnancy registry; and a statement about how the lack of information on fetal toxicity must influence the exclusion criteria for a study.

The NIH and the FDA have worked together to review the paucity of pregnant women enrolled in clinical research [13] and have published a number of recommendations to improve their inclusion in clinical research. These recommendations define pregnant women as a scientifically "complex" population and change the presumption of exclusion, clarify existing regulations, focus on IRB behavior as it facilitates or impedes pregnancy research; and develop a pregnancy research agenda.

In summary, HHS 45 CFR 46 Subpart B provides regulatory guidance for studies of pregnant women and fetuses. This Guidance functions in combination with a number of FDA guidances related to maternal and fetal studies that provide education for IRBs, sponsors and investigators that are necessary to advance the appropriate conduct of research in this population.

9.3 Clinical Pharmacology Considerations

Considerable experience in the use of drugs in pregnant women actually exist related to pregnancy and delivery as well as medical problems of the mother and fetus [14]. Drug therapies during pregnancy and delivery are quite varied and may include anti-microbial agents to treat established maternal infection and prevent neonatal infections, anti-retrovirals to reduce perinatal HIV-1 transmission from the mother to the fetus, corticosteroids to advance fetal lung maturity, antihypertensives to treat pre-eclampsia, anticonvulsants to treat seizure disorders, antidepressants for depression, antibiotics for suspected infection after premature rupture of the membranes to prolong pregnancy and improve neonatal outcomes, tocolytics for premature labor, and oxytocin, ergot alkaloids, anti-emetics during labor, and prostaglandin analogues for postpartum hemorrhage. The fetal and neonatal effects of therapy for the conditions that occur during labor and delivery were previously considered benign, but the possibility of morbidity and mortality involving the mother, the fetus, and the newborn cannot be ignored.

Treatment of perinatal infections is important because of the role infections play in preterm labor and delivery. Ramsey et al. [15] studied the pharmacokinetics of orally administered azithromycin in the term gravid woman. Twenty women who were scheduled for elective cesarean delivery were enrolled. Maternal serum and urine were obtained immediately before the operation and intraoperatively samples of myometrium, maternal adipose tissue, placenta, amniotic fluid, and umbilical arterial and venous cord blood were also obtained. Peak maternal serum azithromycin levels occurred within 6 h (311 ng/mL) of drug administration but declined rapidly over the 24 h after the drug administration. On the other hand, azithromycin levels in myometrial, adipose, and placental tissue were higher (>500 ng/mL) and sustained for up to 72 h after administration. Umbilical arterial and venous serum azithromycin levels were low (19–38 ng/mL) during the first 72 h. Amniotic fluid levels were highest at 6 h (151 ng/mL) and declined rapidly. Considering the sustained high antibiotic levels within myometrium, adipose, and placental tissue, azithromycin may have potential use for the treatment of perinatal infections.

Recognition and acceptance of the need to study mothers and babies during the perinatal period is essential, as recommended by the NIH and the FDA [16–18]. Treatment of pregnant women with various drugs is often based on clinical experience rather than a carefully designed and monitored drug trial that establishes evidence of the proper dose to achieve safe and effective therapy.

Besides the limited study in pregnant women, the late preterm newborn at 34 0/7–36 6/7 weeks is one of the most numerous groups of preterm newborns who are also understudied despite increased morbidity and mortality [19, 20]. Ward has suggested research priorities for drug disposition in late preterm newborns [21]. His suggestions are as follows:

- Disposition of narrow therapeutic index drugs should be studied in late preterm newborns at each week of gestation and each week of postnatal life.

- Pathways of drug disposition, such as cytochrome P450 enzymes and renal excretion by glomerular filtration and tubular secretion, should be studied extensively in the late preterm newborn.
- Factors that accelerate and delay maturation of drug disposition in the late preterm newborn should be identified.
- Animal models of the late preterm newborn, such as preterm sheep or baboons, should be utilized for translational study of pathways of drug disposition.

9.4 Absorption, Distribution, Metabolism and Elimination (ADME) Within the Maternal-Placental-Fetal Unit (MPFU)

Pharmacokinetics for individuals or populations are characterized by the four processes described as absorption, distribution, metabolism, and elimination (ADME). During pregnancy, ADME involves the mother, the placenta, and the fetus designated earlier by Mirkin as the maternal-placental-fetal unit (MPFU) [22, 23].

Most drugs reach the fetus through the placenta by passive diffusion or active transport, but facilitated diffusion, phagocytosis, and pinocytosis may also be involved [24–26]. Diffusion of drugs from the maternal circulation to the fetus generally follows the principles that govern transfer across lipid bilayer membranes. Drugs will pass from a higher to lower concentration driven by the concentration gradient. Passage is facilitated by a large concentration gradient, lipid solubility, presence in an un-ionized form based on pH and pKa, lack of protein binding, and relatively small molecular weight (<500–1000 KDa) [23, 24].

Metabolism must be considered in each component of the MPFU. Changes occur during pregnancy in Phase I enzymes responsible for chemical changes that usually increase polarity of the drug itself and in Phase II enzymes that conjugate drugs to facilitate renal or biliary excretion. As pointed out by Evans and Relling, a small number of CYPs account for the Phase I metabolism of more than 2/3 of prescribed drugs [27]. In order of frequency, they are CYP3A4, 5, 7 > 2D6 > 2C9 > 2C19. They also note that among the Phase II conjugation enzymes, a few account for conjugation of 2/3 of drugs: uridine 5'-diphospho-glucuronosyltransferases (UGTs) > sulfotransferases (SULTs) > n-acetyl transferases (NATs). Each superfamily of these Phase II enzymes include many isoenzymes with different substrate specificity, although the specificity is not as selective as that of the CYPs.

9.4.1 Mother

Large physiologic and anatomic changes occur during pregnancy which can change pharmacokinetics and pharmacodynamics of many drugs throughout pregnancy. Table 9.1 illustrates these changes during each trimester of pregnancy [28].

Table 9.1 Maternal physiologic and anatomic changes that affect pharmacokinetics during pregnancy

	Maternal physiologic changes		
Trimester	**I**	**II**	**III**
Cardiac output	+18 %	+28 %	+33 %
Glomerular filtration rate	+19 %	+37 %	+40 %
Effective renal plasma flow	+38 %	+48 %	+31 %
Creatinine clearance	+28 %	+58 %	+26 %
Uterine blood flow	+923 %	+1567 %	+2721 %
Hepatic blood flow	NC	NC	NC
	Maternal anatomic changes		
Trimester	**I**	**II**	**III**
Total body wt	+6 %	+16 %	+23 %
Total fat mass	+11 %	+16 %	+32 %
Total body water	+11 %	+27 %	+41 %
Plasma volume	+7 %	+42 %	+50 %
Red blood cell volume	+4 %	+20 %	+28 %
Hematocrit	−3 %	−8 %	−14 %
α-1 Acid glycoprotein	−1 %	−22 %	−19 %

Redrawn from Ke et al. [28]

9.4.1.1 Absorption

Drug absorption is reduced by several changes beginning early in pregnancy which reduce maternal drug absorption and lower maternal peak plasma drug concentration. Intestinal motility slows during most of pregnancy, attributed to increased progesterone [29]. Gastric emptying slows, as well, which delays drug reaching the large absorptive area of the small intestine [30]. As pregnancy progresses, the weight of the fetus on the intestine also contributes to slowing of intestinal transit. All of these changes combine to slow drug absorption and reduce the maternal peak concentration. This reduces the maternal/fetal concentration gradient and maternal drug exposure measured by the area under the concentration time curve (AUC).

9.4.1.2 Distribution and Transport

Distribution is affected by many of the changes described in Table 9.1 above. Dramatic increases in the blood volume beginning early in pregnancy expand the distribution volume especially for polar drugs that distribute in the vascular space. This continues so that by 32–34 weeks, plasma volume has expanded by 45–50 % [28, 31]. Conversely, the increase in total body fat that occurs normally during pregnancy will expand the distribution volume for lipophilic nonpolar compounds. The volume of red blood cells increases proportionately less which reduces the hematocrit and binding sites for drugs that distribute into the red blood cells [28, 32]. To meet the metabolic demands of pregnancy, cardiac output increases by 33 %, which

increases renal plasma flow and urine formation. All of these combine to increase uterine and placental blood flow. As drug reaches the placenta, diffusion to the fetus is favored for un-ionized, small, and non-protein-bound molecules. According to the Henderson Hasselbach's equation and the fact that the fetal blood pH is always acidic to varying degrees relative to the maternal pH, basic drugs that equilibrate by diffusion will reach a higher concentration on the acidic (fetal) side of the placenta.

As indicated in Table 9.1, maternal hepatic blood flow does not increase during pregnancy while cardiac output increases by 23 %. Thus, the fraction of cardiac output perfusing the liver actually decreases during pregnancy. The activity of specific cytochrome P450 enzymes varies. While CYP1A2 decreases during pregnancy, CYP2D6 and CYP3A4 increase [33]. The increase in CYP2D6 activity ranged from twofold for clonidine and paroxetine to sixfold for metoprolol as summarized by Isoherranen et al. The activity of CYP2B6 which is relevant to methadone metabolism is confusing. Methadone clearance increases during pregnancy, but that of efavirenz, another substrate for CYP2B6, is unchanged.

9.4.1.3 Elimination

As can be seen from Table 9.1, renal function increases during pregnancy with a 31–48 % increase in renal plasma flow and a 19–40 % increase in glomerular filtration rate. These will combine to increase elimination of drugs that are substrates for tubular secretion, as well as those eliminated by glomerular filtration. To achieve drug exposures comparable to the period before or after pregnancy, the dosage may need to be increased and the dosing interval shortened. Changes in renal transporters during pregnancy have been studied most in animal models.

The effects of changes in bile flow on drug elimination during pregnancy have not been well studied. Many pregnancies are complicated by disorders causing cholestasis that are likely to reduce biliary excretion of specific drugs.

9.4.2 Placenta

9.4.2.1 Absorption

The placenta is a dynamic component of the MPFU during pregnancy as it grows from 1.5 M^2 in the first trimester to 12–14 M^2 at term. [34] During the same time, the villi narrow from 170 to 40 μM which brings fetal and maternal blood closer together, facilitating passive diffusion. Blood flow to the placenta increases 12-fold to reach 600 ml/min, presenting increasing amounts of drugs to the placental villi for diffusion. From studies of oxygen transfer and anatomy, the human placenta is a cross-current diffuser in which maternal flow across the fetal villi occurs from various directions which reduces its efficiency [35]. Studies of mother to fetus transfer of gentamicin by passive diffusion during continuous maternal drug infusion showed that transfer was incomplete in the first trimester for up to almost 6 h, but increased near term so that

fetal and maternal concentrations became equal by 8 h [36]. This illustrates the decrease in placental barrier to transfer as pregnancy progresses toward term.

9.4.2.2 Distribution and Elimination

Transporters within the placenta contribute to maternal/fetal drug transfer which alters the distribution volume for drugs according to their chemical nature and the direction of the transport. The solute carrier superfamily of transporters include monoamine transporters for norepinephrine (NET) and serotonin (SERT); organic cation transporters OCTN1 and 2, OCT3; organic anion OAT4; and organic anion polypeptides: OATP4A1 and OATP2B1 [37]. As shown in Fig. 9.1, these may be located on the maternal or fetal side of the syncytiotrophoblast and transport in either direction or both. Interestingly, p-glycoprotein, the efflux transporter has much higher activity in the placenta early in gestation than near term suggesting it provides greater fetal protection early in pregnancy during organogenesis [38].

9.4.2.3 Metabolism

The placenta plays an active role in drug metabolism for specific compounds. Studies in the near term placenta have shown it can metabolize methadone to 2-ethylidine-1 ,5-dimethyl-3,3-diphenylpyrrolidine (EDDP), an inactive form, by C19 aromatase

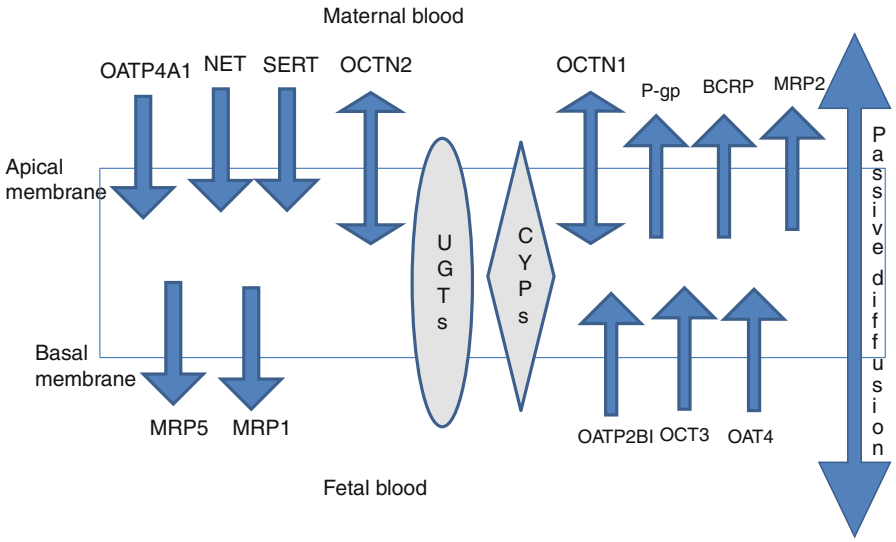

Fig. 9.1 Placental drug transfer and metabolism in the syncytiotrophoblast. Abbreviations: *OAT* organic anion transporter, *OCT* organic cation transporter, *OATP* organic anion assoc. polypeptide transporter, *OCTN* organic cation/carnitine transporter, *P-gp* P glycoprotein (*MDR1* multidrug-resistance transporter 1), *MRP* multidrug-resistant protein, *NET* norepinephrine transporter, and *SERT* serotonin transporter (Adapted from: Rubinchik-Stern et al. [37].)

n-demethylation [39]. This enzyme is also quite active in the metabolism of progesterone, forming multiple metabolites by both microsomal and mitochondrial enzymes [40]. Catecholamine O methyl transferase in the placenta inactivates maternal catecholamines before they reach the fetus, providing protection from wide variations in maternal catecholamines associated with stress and cardiovascular changes.

The unique metabolic activity of the human placenta is illustrated by studies of its metabolism of buproprion, an antidepressant used to assist smoking cessation [41]. Studies of several pathways of metabolism show that in the human placenta, buproprion, is metabolized primarily by 11beta-hydroxysteroid dehydrogenase that reduces it to threo- and erythro-hydrobupropion while in the human liver, it is primarily metabolized by CYP2B6 to OH-bupropion. Maternal/fetal transfer of bupropion evaluated in perfused human placentas at term shows rapid and complete equilibration with a fetal/maternal concentration ratio of 1.07 ± 0.22 [42]. The perfused human placenta is a useful model for evaluation of maternal fetal drug transfer.

9.4.3 Fetus

9.4.3.1 Absorption

Fetal drug absorption is largely dependent on drug passage through the placenta. Fetal skin, however, is quite permeable, especially during the first two trimesters. Drugs that are eliminated into fetal urine, which comprises most of the amniotic fluid could easily be reabsorbed into the fetal circulation by diffusion. This has not received extensive study. The factors involved in placental drug transfer to the fetus are discussed above. These involve primarily diffusion, active transport, and pinocytosis.

9.4.3.2 Distribution

Distribution of polar and nonpolar drugs within the fetus changes as body composition changes during fetal development. The water content of the fetus decreases from around 89 % at 24 weeks gestation to around 74 % water at term. [43] These same studies showed that during this same period, the fat content of the fetus increases from 0.1 % at 24 weeks gestation to 11–12 % at term.

Variations in circulating proteins within the fetus and mother can also influence both transfer of drugs and their distribution. As discussed by Green et al., fetal serum albumin can appear to have low binding for drugs early in gestation, but this may be caused by competition for molecules that are already bound to albumin. [44] Differences in protein concentrations between maternal and fetal circulations can influence drug transfer with a higher concentration facilitating transfer as long as dissociation of the drug occurs rapidly. Human serum albumin (HSA) and α1-acid glycoprotein concentrations are lower in neonates and infants than older children. At birth, HSA concentrations are closer to adults (75–80 %) but α1-acid glycoprotein concentration is half of the adult concentrations [45]. The concentration of HSA in cord blood is 36 g/L as compared to 45 g/L in adult plasma [45]. α1-acid glycoprotein

concentration in cord blood is 0.24 g/L as compared to 0.6 g/L in adult plasma [46]. Studd et al. [47] have mentioned that while albumin concentrations in maternal plasma falls, the fetus produces its own albumin, which gradually increases the fetal plasma albumin concentrations. Depending on the gestational age, it is possible to find fetal:maternal plasma albumin concentration ratios lower, equal, or higher than unity. Studies indicate that binding of drugs to human fetal proteins will vary from drug to drug. For example, Ehrnebo et al. [48] found little binding capacity of fetal plasma for ampicillin, benzylpenicillin, phenobarbital, and diphenylhydantoin. Tucker et al. [49] found that bupivacaine and lignocaine bind less extensively to fetal than to maternal plasma proteins. On the other hand, thiopental, methicillin, and dicloxacillin were found to bind equally to either fetal or maternal plasma proteins [50, 51]. Crawford and Hooi [52] reported salicylate binding to be more extensive in umbilical cord plasma than in the plasma of pregnant women close to term or at term.

9.4.3.3 Metabolism

Fetal drug metabolism is often described as simply low overall, but it is more complex than that. Maturation occurs with different patterns for different Phase I subfamilies of enzymes.

Phase I Reactions: Oxidative Enzymes

The following is a brief summary of the oxidative enzymes involved in Phase I reactions in the human fetal liver.

The CYP 3A subfamily, including CYP 3A4,5 and 7, comprises 30–40 % of the total CYP content in the adult liver and 30–85 % in the fetus [53]. Although no CYP3A4 mRNA was detected, it is active in the fetus in the form of CYP3A7 with a low expression of 3A4 [54]. After preterm birth, CYP3A7 increases for a week before it decreases and is replaced during the first year after birth by CYP3A4, the dominant form in the adult liver. *CYP3A5* is present at a much lower level than CYP3A7 in the liver and is highly variable in some fetuses [55].

CYP1A2 is hardly detectable in early neonatal life but is present at low levels in infants less than 1 year (30 % of adult value) and by the age of 1 year, the levels are 50 % of the adult levels [55]. CYP1A1 mRNA in fetal lung and liver tissue and CYP1B1 mRNA in fetal lung tissue were significantly induced from fetuses whose mothers smoked during pregnancy [56].

CYP2C isoenzymes that are involved in the metabolism of anticonvulsants and nonsteroidal anti-inflammatory drugs as well as warfarin, omeprazole, tolbutamide, diazepam, and propranolol are detectable by 30 weeks in the liver of many fetuses [57]. CYP2C19 appears slightly earlier than CYP2C9. Expression remains low for both until birth, when they both rapidly increase.

CYP2D6. Using tramadol as a model substrate for CYP2D6, Vyhlidal, et al. observed a progressive increase in activity from 25 to 44 weeks PMA [56]. By 44 weeks gestation, CYP2D6 had reached 84 % of adult activity.

9.4.3.4 Phase II Enzymes

Phase II drug metabolism is variable and hard to predict for specific drugs, but these conjugations reactions are often quite important for the elimination of specific drugs that are nonpolar in their parent form. For the UDP glucuronosyltransferases (UGT), UGT2B7, 2B15, and 2B17 mRNA can be detected during the first trimester, but adult liver had 13–36 more UGT2B mRNA than the fetus [58]. The expression of the UGT2B enzymes varied among different organs and among specific enzymes. In the first trimester, fetal lung and kidney had much more UGT2B7 than was found in the liver. In contrast, UGT2B15 and UGT2B17 were both much more abundant in the fetal liver. UGT2B15 showed a steady increase in mRNA during 35–85 days of fetal development in the liver.

Sulfation matures earlier than glucuronidation and is important for the metabolism of drugs as well as endogenous compounds. Sulfation involves transfer of a sulfur group from 3'-phosphoadenosine-5'-phosphosulphate (PAPS) to a hydroxyl or amine group and is an important pathway for metabolism of hormones and neurotransmitters [59]. Activity and abundance of specific sulfotransferases vary widely during gestation. SULT 1A3 involved in sulfation of dopamine was three times higher in fetal liver than in that of adults. Similarly, dehydroepiandrosterone sulfotransferase was sixfold higher in the fetal adrenal than in the adult. In contrast, SULT1A1, involved in sulfation of 4-nitrophenol, was much lower in the fetal liver than in adults. This enzyme is also responsible for metabolism of different forms of thyroid hormones. Pacifici et al. noted wide interindividual variation in the specific sulfotransferases, which may reflect induction or inhibition from xenobiotic exposures or inherited variability.

Variation in fetal drug metabolism was summarized by Pelkonnen et al. in Table 9.2, which shows that by the middle of gestation, the fetus can metabolize many compounds [60]. Broad generalizations that the fetus lacks drug-metabolizing enzymes mischaracterizes their capacity.

9.4.3.5 Perinatal Biliary Function

Bile Acid Metabolism Kimura et al. [61] studied the metabolism of bile acids in 30 pregnant women by analyzing the urinary composition of bile acids during late gestation (weeks 30–41) and again in these women and their newborn infants during the first week after delivery. The mean total bile acid/creatinine ratio in pregnant women decreased from 1.22 micromol/mmol creatinine at 30–32 weeks of gesta-

Table 9.2 Fetus/adult levels of hepatic xenobiotic monoxygenation in human mid-pregnancy (Pelkonen et al. [60])

Substrate	N-dealkylation	Substrate	Hydroxylation
	$(F/A) \times 100$		$(F/A) \times 100$
Aminopyrine	25	Benzo(a)pyrene	2.5
Ethylmorphine	40	Aniline	35
Diazepam	10	Diazepam	14
Prazepam	20	Prazepam	80

tion to 0.15 micromol/mmol creatinine at 6–7 days after delivery. The mean percentage of 1α-hydroxylated bile acids peaked at 27 % at 3–4 days after delivery. In newborn infants, the mean total bile acid/creatinine ratio rapidly increased from 3.39 micromol/mmol creatinine at birth to 54.33 micromol/mmol creatinine at day 7. During this period, large amounts (40–50 %) of unsaturated ketonic bile acids were observed in the infants' urine. The results of the study indicate that during the perinatal period, the formation of polyhydroxylated and unsaturated ketonic bile acids probably represents a mechanism for the excretion of bile salts and that the metabolism of bile acids in both the mother and the infant changes significantly after birth. This may change enteric drug absorption significantly soon after birth.

9.4.4 Difficulties in the Study of Maternal/Fetal Drug Transfer

Paired samples of umbilical cord blood and maternal blood obtained at the time of birth do not accurately reflect the extent of drug transfer from mother to fetus [36]. Differences in the rate of placental passage and different patterns of clearance in the mother and fetus can produce quite different pharmacokinetic patterns of concentration changes over time. Depending on the interval after the maternal dose, the maternal/fetal concentration ratios can vary from almost 3–0.5 as shown in Fig. 9.2 for cephaloridine [62]. Conclusions that the "fetus trapped" or accumulated a particular drug based on the maternal/umbilical cord blood concentration ratio is not justified without a thorough evaluation of the time course of the maternal and umbilical cord concentrations after the maternal dose.

9.5 Maternal Drug Therapy for Fetal Disorders

Several fetal disorders have been treated by administration of drugs to the mother. The delivery of an effective drug concentration to the fetal site of drug action has all the pharmacokinetic challenges outlined above. Advancement of fetal lung maturation was pioneered by Liggins based on observations in sheep of less respiratory distress syndrome (RDS) after treatment of the ewe with corticosteroids to induce delivery [63]. He then proceeded to human studies and showed a significant reduction of RDS in preterm newborns after treatment with a specific corticosteroid formulation that provided both an immediate and a slow release of betamethasone, a halogenated corticosteroid [64]. This formulation was potent enough to induce fetal adrenal suppression and maternal adrenal suppression for 2–3 days after the last dose. In a meta-analysis, Crowley et al. showed that RDS reduction began within 24 h after administration of corticosteroids, a successful fetal therapy [65].

The adrenal suppression of fetal adrenal function by potent corticosteroids has been exploited after identification of a female fetus with a deficiency of an adrenal enzyme leading to virilization in utero. This form of congenital adrenal hyperplasia (CAH) is usually recognized only after the earlier birth of an affected newborn. Early suppression of the fetal adrenal gland in a female fetus can prevent severe

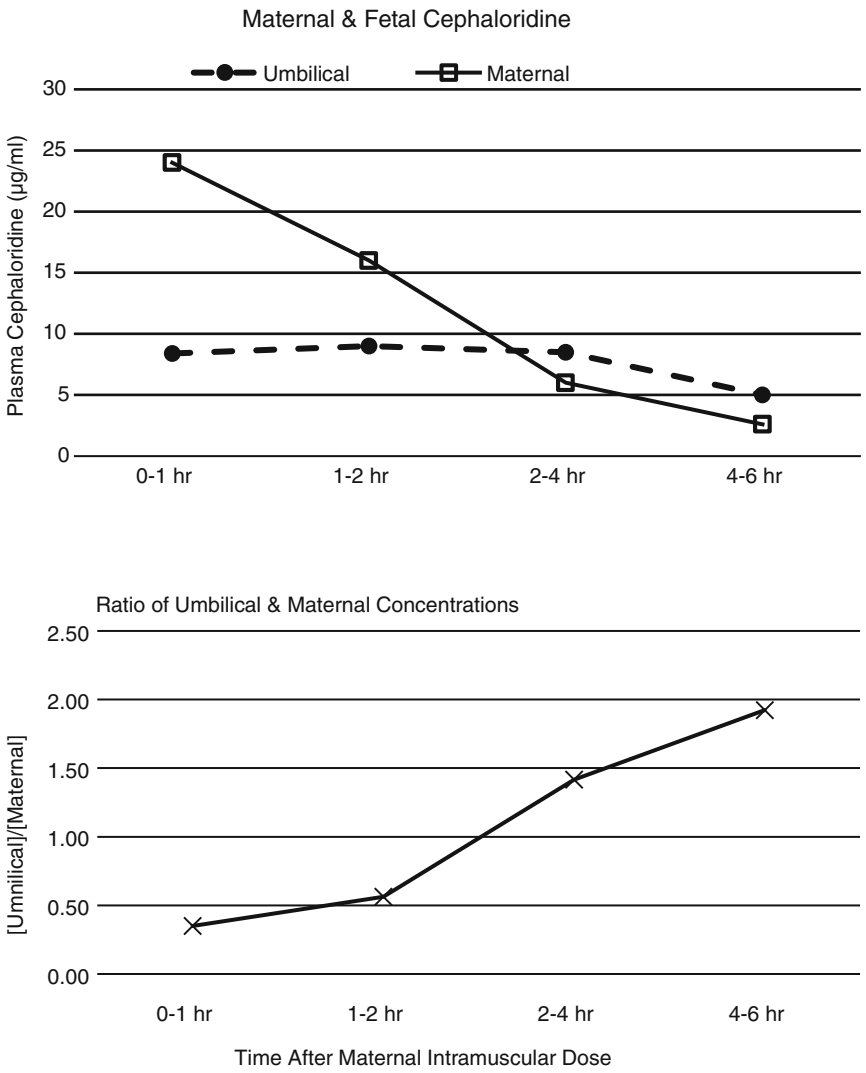

Fig. 9.2 Variation in the ratio of umbilical/maternal cephaloridine plasma concentrations with time after the maternal dose due to slow fetal absorption and elimination combined with rapid maternal absorption and elimination Top: Umbilical and maternal cephaloridine concentrations at delivery after the maternal intramuscular dose. Bottom: Varying ratio of umbilical to maternal cephaloridine concentrations after the maternal dose. (Redrawn from Table II and Figure 4 in Stewart KS, Shafi M, and Williams JD. Distribution of parenteral ampicillin and cephalosporins in late pregnancy. *J Obstet Gynaecol Br Commonwealth* 1973;80:902-908)

virilization requiring multiple surgeries after birth [66]. Treatment with dexamethasone has been accepted worldwide leading to a Japanese guideline for diagnosis and treatment of female fetuses at risk for CAH [67].

Perinatal transmission of HIV can be reduced to 2 % when prenatal pregnancy management is combined with maternal antiretroviral treatment and c-section

Table 9.3 Maternal, fetal, and neonatal toxicity of maternal drug therapy for fetal arrhythmias

Drug	Adverse effect	References
Maternal toxicity		
Digoxin	Palpitations, II° A-V block, Wenckebach	[75]
Quinidine	Nausea, vomiting, tinnitus, diarrhea, ECGΔ, Increased metabolite concentrations	[76]
Lidocaine	Paresthesias	[77]
Procainamide	Widened QRS, Lengthened QT	[77]
Disopyramide	Oxytocic effects, preterm labor	[78]
Proparanolol	Hypotension	[76]
Fetal toxicity		
Digoxin + Verapamil	Death	[79, 80]
Newborn toxicity		
Amiodarone	Hypothyroidism	[81]
Propranolol	Growth retardation, bradycardia, hypoglycemia, primary apnea	[82–84]

Redrawn from Ward [24]

delivery for high viral load with postnatal treatment of the neonate [68]. Bacterial infections associated with premature rupture of membranes and suspected or proven chorioamnionitis have been associated with preterm delivery and are often treated with antibiotics. Ampicillin was frequently administered because of the frequency of group B streptococcus [69], but a recent study found better outcomes with a broader coverage with ceftriaxone, clarithromycin, and metronidazole [70, 71].

Fetal arrhythmias, usually supraventricular tachycardia (SVT) that can cause fetal hydrops and death, have been treated with many different antiarrhythmic drugs, usually administered to the mother to treat the fetus [36]. If fetal or placental hydrops has not developed, digoxin is often effective treatment for SVT. Maternal and fetal concentrations rapidly equalize within 30 min after start of treatment [72]. When hydrops has developed, maternal/fetal transfer is markedly reduced and some clinicians have done direct fetal injections of drugs either intraperitoneally [73] or intramuscularly [74]. During treatment for fetal supraventricular tachycardia, several adverse effects have been reported both in the mother and the fetus as outlined in Table 9.3 [24].

9.6 Neonatal Developmental Pharmacology

Recent studies have expanded our knowledge of neonatal pharmacology, but this area of study seldom keeps pace with the increasing survival of more immature newborns as early as 23–24 weeks, just past ½ of full-term gestation. A comprehensive description of developmental pharmacology of newborns is beyond the scope of this chapter. The reader is referred to several recent comprehensive texts concerning this rapidly changing field [85–88].

9.6.1 Reductive Enzymes

Acetylation In human liver cytosol using p-aminobenzoic acid as a substrate, Pacifici et al. [89] showed that acetyltransferase activity in human adult liver is threefold higher than fetal liver.

N-demethyltransferase N7-methylation of theophylline to produce caffeine in neonates is well developed but oxidative demethylation is deficient and develops over time [55].

Thiomethyltransferases Hepatic thiomethyltransferases is generally one order of magnitude higher than in extrahepatic tissues both in fetuses and adults. Thiomethyltransferases activity is present in fetal liver, but the activity in adult liver is sixfold higher [90]. Renal activity of thiomethyltransferases is comparable with that of lung and intestine in the fetus, whereas renal thiomethyltransferases in adult tissues is three- to fourfold more active than in the other extrahepatic tissues [55].

Thiopurine-S-methyltransferase Thiopurine-S methyltransferase activity is present in the fetal liver, but adult liver has threefold higher activity than the fetal liver. The hepatic and renal thiopurine-S-methyltransferase activities are similar in human fetuses, whereas the renal activity in adults is twice that of hepatic activity [91].

Conjugation with Amino Acid Conjugation of xenobiotics carboxylic acid with endogenous amino acids is an important pathway in the metabolism of a number of compounds [55]. In humans, the most frequently observed amino acid conjugates are glycine and glutamine, whereas taurine conjugation is a minor one [55]. Conjugation with glycine is fairly well developed in fetal liver [92].

Conjugation with Glutathione Glutathione conjugation is catalyzed by cytosolic glutathione S-transferase. Epoxides may be metabolized by this pathway [55]. Pacifici and Rane [93] using styrene oxide as a substrate studied glutathione S-transferase activity in a number of human fetal tissues. The activity of glutathione S-transferase was found to be uniform across liver, adrenals, lungs, and kidneys. Pacifici et al. [93] further investigated glutathione S-transferase activity using benzopyrene-4, 5-oxide as a substrate. These authors found that the glutathione S-transferase activity in the cytosol of fetal liver was 60 % of that in the cytosol of adult liver, whereas the activity in other fetal tissues was similar. In the fetal lungs, glutathione S-transferase activity was higher than in adults [93].

9.7 Summary

Clinical pharmacology studies in the mother and child should be driven by information derived from sound scientific study. While the regulatory environment is only now ready to collect this information prospectively, considerable information exists to allow for the development of clinical pharmacology studies in both marketed drugs and those drugs under development.

Disclaimer The content of this chapter is the opinion of the authors and does not represent the position of the US Food and Drug Administration.

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