Review Article

Theme: Challenges and Opportunities in Pediatric Drug Development

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Strategic Biomarkers for Drug Development in Treating Rare Diseases and Diseases in Neonates and Infants

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Abstract. There are similar challenges in developing a product designed to treat patients with a rare disease and drugs to treat critically ill neonates and infants. Part of the challenge in developing such products as well as identifying the optimal dosing regimen for the treatment of young children arises from the complex interrelationship between developmental changes and changes in biomarkers responsive to drug therapy. These difficulties are further compounded by our lack of understanding of the key physiological factors that cause the differences in clinical responses between adults and neonates and infants. Regulatory efforts have succeeded in overcoming these challenges in many areas of pediatric and orphan drug development. Strategic applications of biomarkers and surrogate endpoints for the development and approval of a product used to treat an orphan disease will be highlighted with examples of approved products. Continued efforts are still needed to fill in our knowledge gap and to strategically link biomarkers and surrogate endpoints to clinical responses for rare diseases and diseases affecting neonates and infants.

KEY WORDS: biomarkers; infants; neonates; rare diseases.

INTRODUCTION

Drug development in any small patient population is challenging. The limitation in patient numbers presents an early obstacle in identifying an appropriate dose, extends to problems in demonstrating efficacy of the product in treating the disease, and is magnified by an inability to identify the treatment-associated adverse effect profile. Achieving effective and safe pharmacotherapy for pediatric patients is a goal of all drug development stakeholders worldwide. However, there are still limited data to guide dosing of drugs in pediatric patients, especially neonates. The European

Medicines Agency recently published the results of a comprehensive survey on the pediatric use of medicinal products in Europe (1). The survey revealed that of all prescriptions for pediatric patients, off-label use constituted 45–60% of the total number of prescriptions and reached up to 90% in premature neonates. Similarly, off-label use of drugs for treating pediatric illness, particularly for rare diseases, is still a problem in the USA as almost half of drugs are still not labeled for pediatric patients (2). To address the important need to obtain important prescribing data for infants and children, Congress passed legislation initially under the Food and Drug Administration Modernization Act of 1997. Subsequently, incentives for drug manufactures were expanded in 2002 under the Best Pharmaceuticals for Children's Act (BPCA), and requirements for pediatric studies under the Pediatric Research Equity Act (PREA) were established in 2003. BCPA and PREA are now permanent under the Food and Drug Administration Safety and Innovation Act (FDASIA) (3), which includes provisions for incentives to be given to drug manufacturers who perform studies in infants and children. Since the implementation of BPCA and PREA, progress has been made, and the FDA's internal statistics show that over 450 products include pediatric labeling information as a result of BPCA and PREA, with some labeling related to dosing and others to safety or lack of efficacy.

Development of drugs to treat rare diseases, including inborn errors of metabolism (IEM) disorders, shares similar challenges to drug development for treating diseases in pediatric populations. Though IEM disorders affect both

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children and adults, many patients with IEM disorders die at a young age. As a result, many of these diseases have populations that mainly consist of children and young adults. Thus, drug development for these disorders must include data to guide dosing in infants and children. This article will review advances in application of biomarkers to drug development by focusing on the example of IEM disorders that affect neonates and infants. The role of biomarkers in early clinical development and as potential endpoints in clinical trials in IEM disorders will be discussed. Thoughtful development of biomarkers in drug development may provide a path forward for more effective products used in the treatment of infants and critically ill neonates.

DEVELOPMENT OF PRODUCTS FOR ORPHAN INDICATIONS

The Orphan Drug Act defines an orphan disease as one that affects fewer than 200,000 people in the USA (4). However, there are over 7,000 rare diseases, and it is estimated that over 25 million patients in North America are affected by a rare disease (5). Thus, finding and developing treatments for rare diseases is both an important scientific and public health issue. Importantly, the Orphan Drug Act does not provide for a different standard of evidence for approval of a product used to treat an orphan disease. Therefore, in order for a product developed to treat an orphan disease to be approved, there must be substantial evidence of effectiveness/clinical benefit. Substantial benefit has been defined as being able to distinguish the effects of the drug from other influences, such as spontaneous change in the course of the disease, placebo effect, or biased observation, in adequate and well-controlled clinical trials (6). The role of biomarkers used during drug development plans for drug or biologic products to treat orphan diseases will be discussed below. Unique examples will be highlighted below to provide informative references.

Use of Biomarkers in Early Drug Development

A biomarker has previously been defined as “A characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention” (7). Biomarkers have been used extensively in clinical practice. For example, serum cholesterol is a biomarker commonly used in clinical practice as changes in the dosage of a drug used to treat hypercholesterolemia may be made based on the patient's serum cholesterol level.

Biomarkers are also potentially useful in all phases of drug development. Evaluation and application of biomarkers can help to refine a dose, dose interval, and appropriate population during early-phase clinical development of a product. They are of particular interest in the development of drug and biologic products used to treat orphan diseases because conducting long-term clinical trials in patients with IEM diseases to demonstrate the clinical efficacy of a product are often not feasible. However, the acceptability of a biomarker for use in clinical trials requires careful scrutiny and a clear physiological understanding and statistical meaningful depiction of the changes in the biomarker in the

specific disease process. Often, prospective natural history studies are undertaken during the drug development for rare diseases to better understand disease progression and to characterize the relationship between specific biomarkers and disease progression. Well characterized, relevant biomarkers may potentially be used either as clinically meaningful endpoints in phase 3 trials or as surrogate endpoints that are likely to predict clinical benefit. Examples of biomarkers used previously as both clinically meaningful and surrogate endpoints are described below.

Clinically Important Changes in Relevant Biomarkers in Developing Drugs for Treating Orphan Indications

As described in the previous section, biomarkers may be useful in early-phase development of products used to treat orphan disease. Additionally, important and clinically meaningful changes in relevant biomarkers may also be used to provide substantial evidence of efficacy in clinical trials for orphan diseases, and such endpoints may be used as primary efficacy endpoints in phase 3 trials. One such example is the successful use of the biomarker, hemoglobin, as a clinical efficacy endpoint during phase 3 trials to evaluate products used to treat type 1 Gaucher disease. Gaucher disease is a lysosomal storage disease caused by a deficiency in the lysosomal enzyme glucocerebrosidase. A deficiency or absence of this enzyme affects multiple organ systems due to an accumulation of glucocerebroside in multiple organs including the liver, spleen, bone marrow, and brain. Clinical manifestations include hepatosplenomegaly, hypersplenism, anemia, thrombocytopenia, bone disease (including pain, fractures, osteopenia, and osteonecrosis), and lung disease. Although type 1 Gaucher disease decreases life expectancy, progression may take years or decades. Therefore, measuring an effect of any treatment on survival in type 1 Gaucher disease would be difficult. However, the change from baseline in hemoglobin concentration would be clinically meaningful in light of the natural history of untreated Gaucher disease. Therefore, normalization of hemoglobin count was considered clinically meaningful in type 1 Gaucher disease and could be used to support full approval. In contrast, clearance of the biomarker glucocerebroside from tissues, though specific to type 1 Gaucher disease, has not been associated with a long-term clinical benefit. Thus, normalization of hemoglobin has been used as a clinical endpoint in trials leading to the approval of four therapies in type 1 Gaucher disease: purified human glucocerebrosidase (Ceredase®), imiglucerase (Cerezyme®), gene-activated human glucocerebrosidase (Velaglucerase®), miglustat (Zavesca®), and taliglucerase alfa (Elelyso®).

Use of Biomarkers as Surrogate Endpoints

An important distinction must be made between the evaluation of a clinically meaningful endpoint *versus* evaluation of a surrogate endpoint. As described above, for type 1 Gaucher disease, normalization in the biomarker hemoglobin was considered clinically meaningful and has supported the effectiveness of several products used to treat type 1 Gaucher disease. In contrast, a surrogate endpoint is defined as “A biomarker that is intended to substitute for a clinical

endpoint. A surrogate endpoint is expected to predict clinical benefit or harm, or lack of benefit or harm based on epidemiologic, therapeutic, pathophysiologic, or other scientific evidence.” (7). Thus a subset of biomarkers may be suitable for use as surrogate endpoints; however, not all biomarkers, even clinically useful biomarkers, are suitable for use as surrogate endpoints.

As stated earlier, biomarkers may be useful in establishing appropriate target dosing or for evaluation of potential clinically meaningful endpoints during early-phase drug development. Additionally, for products intended to treat serious or life-threatening illnesses, many of which are also orphan diseases, specific biomarkers may be used as surrogate markers in phase 3 clinical trials to support the efficacy and/or safety of the product. Under “accelerated approval” regulations (21CFR 314 Subpart H and 21CFR 601 Subpart E), marketing approval can be granted based on a surrogate endpoint “that is reasonably likely, based on epidemiologic, therapeutic, pathophysiologic, or other evidence, to predict clinical benefit or on the basis of an effect on a clinical endpoint other than survival or irreversible morbidity” (6). However, approval under this regulation is subject to the requirement that the applicant study the drug further, to verify and describe its clinical benefit, where there is uncertainty of the relationship of the surrogate endpoint to clinical benefit, or of the observed clinical benefit to ultimate outcome. Use of surrogate endpoints under the accelerated approval regulations is often an attractive alternative in the setting of rare, life-threatening diseases.

Use of a biomarker as a surrogate endpoint has also been used as a basis for accelerated approval for agalsidase beta, a product used to treat Fabry disease. Fabry disease is a rare lysosomal storage disease caused by a deficiency or absence of α -galactosidase A. Deficiency or absence of this enzyme leads to accumulation of globotriaosylceramide (Gb3) in lysosomes of affected tissues, including the brain, heart, kidneys, peripheral nerves, and skin. Clinical manifestations of Fabry disease include stroke, myocardial infarction, kidney failure, and painful neuropathy. Like type 1 Gaucher disease, Fabry disease progression is slow, and differences in clinically meaningful endpoints such as survival, or time to events such as kidney failure, myocardial infarction, or stroke, could take years to decades to measure. Gb3 deposition in the renal interstitial capillary endothelial cells is believed to produce injury to the kidney, ultimately leading to kidney failure (8). Therefore, clearance of Gb3 from renal interstitial capillary endothelial cells could be considered a suitable surrogate endpoint to support accelerated approval because it would be reasonably likely to predict a clinical benefit, that is, a decrease in time to development of end-stage kidney disease. Clearance of Gb3 was used to support the approval of agalsidase beta (Fabrazyme®). In keeping with the accelerated approval regulations, a post-approval study to verify the clinical benefit of this product was required as a condition of approval (9).

Reliance on surrogate markers may facilitate development of life-saving products to market in a timely fashion. However, there are important challenges in the reliance of biomarkers as adequate surrogate markers, especially in rare diseases. Often, the natural history of rare diseases is not well understood. Therefore, the relationship between a potential

surrogate and a clinical outcome is not well established. Even when the relationship between a biomarker and a clinical outcome is understood, the change in the biomarker may not completely account for the effect of a therapy on the clinical endpoint. Thus, a biomarker may capture only part of the effect of the treatment. In such cases, a biomarker would not be considered a suitable surrogate endpoint for assessment of efficacy of a treatment for the disease (7). For example, mucopolysaccharidosis type 1 (MPS 1), or Hurler's syndrome, is a multisystemic disease caused by a deficiency of a lysosomal enzyme, α -L iduronidase. Deficiency of this enzyme leads to accumulation of glycosaminoglycans, heparin sulfate, and dermatan sulfate, in affected tissues, including the brain. Clinical manifestations include growth retardation, hepatosplenomegaly, and progressive cognitive impairment. Laronidase (Aldurazyme®) is an enzyme replacement therapy approved for the treatment of MPS 1. Urinary clearance of glycosaminoglycans is a biomarker that was evaluated in the clinical trials for laronidase. Indeed, treatment with laronidase produced substantial urinary clearance of glycosaminoglycans. However, enzyme replacement therapy with laronidase does not affect the progressive cognitive impairment associated with MPS 1 because laronidase does not cross the blood-brain barrier. Thus, urinary clearance of glycosaminoglycans is a biomarker that may only capture part of the effect of treatment and would not be a suitable biomarker for the CNS functional changes in MPS 1. Indeed, measurement of CNS functional changes is difficult in MPS 1 because of the slow progression and because disease-specific tools for measurement of CNS changes have not been developed (10). Thus, reliance on a single biomarker in a disease with multisystem involvement (*i.e.*, clinically important CNS and systemic manifestations) may not predict improvements in all important clinically meaningful manifestations of the disease.

Recently, there has been interest in developing a formal qualification process for use of biomarkers in clinical drug development. The formal qualification for candidate biomarkers is complex and is beyond the scope of this article. However, guidance for the qualification of biomarkers is available (10). Full qualification of biomarkers for use in clinical drug development may take several years. However, use of biomarkers that have not been fully qualified may still be of use during drug development for orphan diseases (*i.e.*, in early-phase development or as potential surrogate markers under accelerated approval regulations) as described above.

In summary, use of suitable biomarkers may aid in the efficiency of clinical development programs for therapies to treat rare diseases. However, evaluation of suitable biomarkers must be approached with rigor, to avoid reliance on an inaccurate biomarker or surrogate endpoints which could lead to ineffective or unsafe therapies for patients with rare diseases.

INBORN ERRORS OF METABOLISM DISORDERS VERSUS CRITICALLY ILL NEONATES/INFANTS WITH OTHER DISEASES

Patients with IEM disorders often require lifelong treatment, and diagnosis is frequently made soon after birth. Critically ill neonates and infants are referred to herein as

having a disease other than an IEM disorder. Critical illness in neonates may include acute renal failure, acute hepatic failure, circulatory failure, respiratory failure, and intestinal failure. For both IEM disorders and critical illnesses in neonates and infants, clinicians are often faced with the challenges of choosing the right drug and right dose.

There are similarities and differences in the development of drugs and biologic products used to treat IEM disorders *versus* to treat critically ill neonates and infants, as summarized in Table I. Development of drugs and biologic products to treat both of these populations is uniquely hampered by the small number of patients that are available for clinical study. When developing a drug used to treat an IEM disorder, initial studies may need to include both children and adults. For some IEM disorders, there may be only pediatric patients available for clinical trials since patients may not survive through adulthood. On the other hand, when a drug which is being used or under development to treat critically ill neonates and infants is efficacious in adults for the same indication, the possibility of extrapolation of efficacy can be considered (11). Extrapolation is permissible when the course of disease and the effect of the drug are the same for pediatric patients and adults (or another pediatric age group). However, extrapolation of efficacy must be supported by additional information on dosing and safety. Dosing and safety information from adult patients cannot be extrapolated to in the pediatric population of interest (12).

In addition to supporting the extrapolation of efficacy, matching adult pharmacokinetic exposure is often one approach for selecting a dose for neonates and infants. When the pharmacodynamic and pharmacokinetic correlation is known and the pharmacodynamic response correlates with clinical efficacy, exposure data can be considered in dose selection. Designing appropriate dosing schemes for the various age groups requires considerations of developmental biomarkers to treat orphan diseases and other pediatric illnesses, for either clinical use or pharmaceutical development. The section below will focus on discussion of developmental biomarkers for applications to achieve adequate clinical efficacy in neonates and infants. Such knowledge is important for treating IEM disorders as well.

DEVELOPMENTAL BIOMARKERS FOR NEWBORNS AND INFANTS

There are tremendous developmental changes starting from birth to infancy and beyond. Not only are organs maturing in function but also changing in size. In addition to these physiological changes that can affect the extent of variability in the exposure of a drug substance, the pharmacogenetics of drug-metabolizing enzymes can also be a contributing factor and should be weighed in as well. The relationship among age, body size, and ontogeny of physiological factors is complex and nonlinear. The clinical significance of these factors will be highlighted below.

Ontogeny and Pharmacogenetics

Knowledge of pediatric clinical pharmacology is essential to the design and conduct of informative pediatric trials. Differences in physiological factors between children and adults include total body water, protein binding, cytochrome P450 ontogeny, gastrointestinal motility and pH, and organ (*e.g.*, renal and hepatic) function, all of which can cause clinical changes in the absorption, distribution, metabolism, and elimination of drugs throughout childhood. In addition, dosing requirements vary for pediatric patients based on age, due to developmental changes in drug-metabolizing enzymes and transporting proteins among other physiological factors, which ultimately impact the pharmacokinetics (PK), pharmacodynamics, and clinical outcomes of a drug (13,14).

Glomerular filtration contributes to the renal elimination of drugs, and the developmental changes in the glomerular filtration rate can be used as a biomarker for predicting the total body clearance for those drugs that are mainly eliminated *via* glomerular filtration. Rhodin *et al.* recently characterized in detail the developmental changes in glomerular filtration as a function of postmenstrual age after correcting for size-related differences in study subjects by accounting for weight *via* an allometric power model (15).

The maturational development of many drug-metabolizing enzymes has been characterized. Examples include the cytochrome P450 (CYP) subfamily 3A (16,17), the enzymes

Table I. Comparison of Drug Development for Treating IEM Disorders and Critically Ill Neonates/Infants

	Critically ill neonates and infants	IEM disorders
Drug candidate being developed	Approved for treating adults with the same indication	Not approved in adults for the same indication
Clinical trial population	Depends on the disease being studied, may be small	Usually not yet approved for the orphan indication
Clinical efficacy trial	Extrapolation of efficacy from adults with supporting safety data may be considered. No extrapolation of dose and safety profiles	Adequate and well-controlled trial(s) required
Efficacy	Matching adult exposure if extrapolation of efficacy is possible	Clinical endpoints, clinically relevant biomarkers, or surrogate endpoints
Pharmacokinetics	Sparse sampling scheme and population pharmacokinetic analysis	
Exposure/dose relationship	Varies with developmental changes	
Safety profile	May be informed by clinical trials in adults with the same indication, depending on exposure	Generally unknown in the disease population; reference information available if previously approved for other indications

IEM inborn errors of metabolism

CYP2C9 and 2C19 (18), the flavin-containing monooxygenases 1 and 3 (19), and various members of the uridine 5'-diphosphate-glucuronosyltransferase superfamily (20,21). While most of these enzymes show a reduced activity prenatally and in neonates compared to adults, the trajectory of developmental maturation of each individual enzyme is unique (22,23). In addition to the ontogeny of phase I and II drug-metabolizing enzymes, genetic variations have also been shown to contribute to the variability in the pediatric dose-exposure relationship and consequently to the variability in the clinical efficacy and safety of drugs (24). CYP2D6 and thiopurine S-methyltransferase are two notable examples that have been discussed in this context (25). In children, the CYP 2C19-specific content reportedly was 60-fold lower in 8–23-week olds than in 5-month to 18-year olds and varied 35-fold in 0–5-month olds (18). On the contrary, less is understood about the ontogeny of drug transport proteins. Preliminary data by Tang *et al.* (26) suggested a relatively fast achievement of the adult level for P-glycoprotein but a protracted increase in the expression of MRP-2 throughout the first 6 months of life.

Age

In population pharmacokinetic analyses for pediatric patients, age is usually an essential covariate for estimating drug clearance. Age is not the underlying cause for the differences in pediatric drug clearance but rather is a surrogate for the developmental trajectory of physiological processes involved in drug disposition. Thus, *a priori* inclusion of the ontogenic trajectory of these processes in a modeling approach may prospectively explain much of the developmental changes in drug disposition, thereby providing the mechanistic basis for predicting the age dependency of drug clearance. For example, Nong *et al.* (27) integrated the ontogeny of CYP2E1 as a major metabolism pathway for toluene into a physiologically based pharmacokinetic model for the prediction of toluene clearance as a function of postnatal age. Further prospective use of the ontogeny data of drug-metabolizing enzymes and drug transporters in combination with physiologic pharmacokinetic modeling and systems biology approaches will allow us to more precisely predict the likely behavior of drug substances in the pediatric population across the age strata, including term and premature neonates (28).

Developmental Pharmacodynamic Biomarkers

Much less is known about the developmental pharmacodynamics of drugs as few studies compare neonates and adults or older children. Marshall *et al.* (29), for instance, showed in an *ex vivo* assay of peripheral blood monocytes that neonates had a much higher sensitivity compared to adults in responding to the immunosuppressive effect of cyclosporine. Similarly, Laer *et al.* (30) showed that the antiarrhythmic effect of sotalol quantified as QTc prolongation per unit sotalol plasma concentrations was substantially higher in neonates compared to adults, with an intermediate sensitivity in infants under 2 years of age. Interestingly, according to Nexium® (esomeprazole) labeling, despite a similar pharmacodynamic response (the percent time with

intra-gastric pH>4) observed for the effective regimen in adults, infants 1–11 months failed to show significant improvement in their gastroesophageal reflux disease (GERD) symptoms. Integration of pharmacokinetic as well as pharmacodynamic developmental trajectories into dose-exposure-response models may improve our ability to develop and derive age-appropriate pediatric dosing recommendations for clinical trials (31).

Body Size

Body size has an overarching effect on clearance and volume of distribution, and body size measures such as weight or body surface area are strongly correlated with the ontogeny of drug-metabolizing enzymes and drug transporters (32). Due to this strong collinearity between body size and developmental biomarkers and due to the overwhelming effect of body size on clearance and volume of distribution, the effect of body maturation on drug disposition cannot be adequately determined in a concurrent analysis of the size-related effects. The challenges and limitations to concurrently analyzing the effect of collinear covariates are well described (33). To overcome this dilemma, body size is frequently included *a priori* in pharmacokinetic models using an allometric modeling approach (32, 34, 35). While this approach makes the strong assumption of the correctness of the allometric size model, it is a pragmatic analysis pathway that allows identifying and quantifying the effect of maturational processes in the presence of size changes that would otherwise overlay and obscure most developmental effects on pharmacokinetic parameters (36).

CLINICAL PHARMACOKINETIC STUDIES IN NEONATES AND INFANTS

If the course of a disease and the effect of a drug are sufficiently similar in both adult and pediatric patients, regulatory agencies such as the FDA may conclude that the drug's pediatric effectiveness can be extrapolated from adequate and well-controlled studies in adults with supportive data, such as pediatric pharmacokinetic studies. In order to support extrapolation of efficacy, the pediatric pharmacokinetic exposure of an age-appropriate formulation using the designed dosing regimen must be comparable to that in adults. Furthermore, a pharmacokinetic study may not be needed in each pediatric age group if data from one age group can be extrapolated or interpolated to another age group. However, drug safety and dose cannot be extrapolated. Early pediatric drug development often includes pharmacokinetic and tolerability assessment studies over at least two dose levels when adult and pediatric indications are perceived to be similar so that pharmacokinetic characteristics in relation to dose can be compared to adult patients.

Consideration of pediatric clinical pharmacology including the aforementioned biomarkers is important for the design of the early pediatric pharmacokinetic clinical trials (37). The primary goals for pediatric PK trials are to determine the pharmacokinetic and tolerability profile with an adequate sample size and an informative sampling scheme, and to understand the dose/exposure relationship across the age strata. The scheme of age strata is typically designed

based on our understanding of the ontogeny of the key drug-metabolizing enzyme(s) involved in eliminating the drug under investigation. Increasingly, pediatric efficacy and safety trials over at least two dose levels with an adequate statistical power and well-defined clinical primary endpoints are required along with a population pharmacokinetic exposure and response analysis. Pediatric studies, including pharmacokinetic and clinical efficacy/safety studies, are typically conducted sequentially starting with older patients (*e.g.* adolescents) before enrolling the younger age groups. The goal for staggered enrollment is to evaluate safety data in older children before exposing younger children to a drug product, as well as to obtain additional preliminary efficacy data.

For pharmacokinetic studies, adequate blood samplings to characterize the full plasma concentration/time profile are typically needed. However, due to limited total blood volumes in the youngest pediatric patients (<2-year olds and particularly neonates), traditional PK studies may not be feasible. Most institutional review boards limit blood collection during a single trial to 3 mL/kg, and obtaining more than two to three blood samples from a neonate or younger child may not be possible. For this reason, sparse sampling techniques along with population PK are an alternative. A commonly employed strategy is to randomize subjects to different (two or more) sampling schemes so that the pooled dataset is adequate for estimating the key pharmacokinetic parameters, such as clearance and half life. Ideally, the overall samplings from the study population should cover at least three half-lives of a drug. A more recent study has demonstrated that even scavenged blood samples in premature infants can be used to assess PK through population PK analysis (38).

Recent applications of the physiologically based pharmacokinetic (PBPK) models allow incorporation of age/size dependencies for dose “scaling,” thanks to the availability of physiologic parameter databases. PBPK models which consider body size and developmental and age-dependent physiologic changes are of great utility for individualized medicine; even then, adult data are not available (39–41).

Improvements in pediatric clinical trial designs are still needed to increase the chance that clinical efficacy can be demonstrated. For example, a recent systemic review of five clinical trials involving approximately 110 infants by van der Pol, *et al.*, concluded that proton pump inhibitors (PPIs) are not effective in treating GERD in infants. The key reasons are that acid reflux has never been demonstrated in infants with symptoms of GERD, and gastric pH increase (the effect of PPIs) correlates poorly with efficacy of treating GERD (42). Antiemetic drugs are another example where demonstration of clinical efficacy in infants and neonates is challenging since the patients cannot verbally communicate the feeling of nausea, and thus, endpoints must rely on objective observations such as frequency of vomiting or retching. The belief that the qualification of surrogate biomarkers for a clinical primary endpoint is needed to shorten the development time of a drug for pediatric use is novel but remains a great challenge to achieve such a goal for all diseases. Integration of our clinical knowledge about the complexity of a disease and the primary endpoint(s) of an indication with modeling and simulation technology by taking

into account pediatric clinical pharmacology is a stepping stone for achieving future successes in treating diseases in children.

OPTIMIZING CLINICAL CARE FOR CRITICALLY ILL NEONATES AND INFANTS

Treating the neonatal population remains very challenging because there is rarely any evidence-based prescribing information available for reference. The choice of a specific dosing regimen of a drug for this population based on expert opinion is an outdated approach but unfortunately is still a common practice due to lack of data. Empiric dosing may in fact be incorrect and potentially unsafe. Lacking sufficient PK information in neonates to guide the dosing of milrinone in neonates with hypoplastic left heart syndrome, Zuppa *et al.* conducted a clinical pharmacokinetic study which changed the practice at their institute (43). The authors stated that “Post-operatively, neonates now initially receive a continuous infusion of 0.2 µg/kg/min, instead of 0.5 µg/kg/min. The dose rate of the infusion is titrated up once urine output improves, and clinical exam warrants an increase in dose.” In addition, another recent population pharmacokinetic study modified the design of the dosing regimen of milrinone in preterm infants in order to optimize systemic blood flow immediately after birth (44). Of note, the safety and efficacy of milrinone has not been established in pediatric patients. Nonetheless, these pharmacokinetic studies and population pharmacokinetic analysis have impacted clinical care. Such studies should be encouraged to produce important information to guide the care of future patients within the same institution and across institutes. Argatroban, a direct thrombin inhibitor, is an example where labeling information of pediatric dosing has been added following a population pharmacokinetic analysis of 15 seriously ill pediatric patients which revealed that seriously ill pediatric patients had 50% lower clearance compared to adults (45).

REGULATORY EVOLUTION IN PEDIATRIC DRUG DEVELOPMENT

The BPCA and the PREA provide the regulatory framework for obtaining pediatric studies. Under BPCA, FDA is authorized to issue a pediatric Written Request that describes any necessary studies in the pediatric populations to show an on-patent drug's clinical benefit in children. These studies can be related to both on- and off-label indications. Under this voluntary process, a drug holder may be granted pediatric exclusivity (the “carrot”). The PREA mandates that pediatric studies be conducted for certain new drugs and pediatric assessments be submitted to inform drug labeling. PREA (the “stick”) is retroactive to April 1, 1999. These laws, reauthorized under the Food and Drug Administration Amendments Act of 2007, are now permanent as a result of FDASIA 2012. In addition, the results of completed pediatric studies, whether positive, negative, or inconclusive, must be included in the approved labeling of the product. The FDA applies the same scientific rigor when reviewing the reports and protocols of pediatric studies as is done for adults

Success Measure of BPCA and PREA

FDA's internal statistics show that over 450 products include pediatric labeling information as a result of BPCA and PREA. Interestingly, only 20% of the studies yielded new dosing recommendations. Also, only one labeling update has included premature infants (46). Nonetheless, these results submitted per pediatric Written Requests issued by the FDA have provided us with invaluable information, which would not have otherwise been available, to understand the similarity and differences between adult and pediatric patients regarding the pharmacokinetics of drugs (47). Several of the notable findings include: (1) lower apparent oral clearance per kilogram for some therapeutic agents in pediatric patients, (2) higher clearance per kilogram for other drugs and age groups, and (3) some drugs are better dosed by body surface area than by body weight.

Important information about the lack of efficacy or safety concerns of accepted treatments has also been included in labeling as a result of the pediatric legislation. For example, imiquimod (Aldara®), while approved for treating genital and perianal warts in patients older than 12 years of age since 2007, was frequently used for treating molluscum contagiosum (MC) in younger children. A randomized controlled clinical trial in 2–12-year olds failed to demonstrate any clinical efficacy for treating MC. As a result, Aldara's label specifically indicates that the drug is not effective in treating MC, thus discouraging off-label use by pediatricians. Thus, the labeling changes following pediatric studies not only provide important safety information but also disseminate negative clinical trial information.

In order to meet the requirements of FDASIA, the pediatric plan must be discussed early, soon after the end of phase 2 (3). In addition, use of modeling and simulation has been implemented to help improve the quality of pediatric clinical trials. All of these efforts are helping timely development of effective and safe medication for pediatric patients.

Collaboration between FDA and EMA

FDA and the European Medicines Agency (EMA) share a common goal, that is a drug will only be approved for the proposed indication(s) when demonstrated efficacious and safe in the targeted population(s). There is also a need for between-agency collaborations to assist pediatric drug development because (1) the pediatric population, as compared to adults, is smaller, (2) pediatric trials are often limited by the fact that children cannot volunteer to participate in clinical trials, (3) there are particular safety and ethical concerns for involving children in clinical trials, and (4) more experienced clinical sites are needed to have a sufficient number of patients to complete these trials. To assist pediatric drug development beyond the regulatory boundary, FDA and EMA have ongoing information exchange through monthly teleconference meetings and through a secure link, Eudralink.

LOOKING INTO THE FUTURE

There are still many orphan diseases for which individual disease populations are small and for which there are no safe and effective treatments. Inborn errors occur early in life and

are on the list of urgent needs that regulatory agencies need to work collaboratively to achieve successes in the near future. In addition, although PREA and BPCA have been successful in improving and increasing the safety, effectiveness, and dosing data available in product labeling for older pediatric populations, there is still a substantial need for this information for neonates and infants. New strategies to encourage developing drugs for these vulnerable populations are needed. Identifying clinically relevant biomarkers and surrogate endpoints for approval of drugs or biologic products to individual orphan diseases is very critical and needs all the stakeholders to work concertedly to successfully treat and manage these diseases.

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