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POSOLOGY: DRUG DEVELOPMENT IN PEDIATRICS

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ABSTRACT
Reluctance to enroll pediatric subjects in clinical trials has left gaps in information about the dosing, safety, and efficacy of medications. A pediatric population is a diverse group comprising different subgroups and liquids being the most preferred dosage form for children, especially of lower age. However, in the absence of suitable or labeled dosage forms, the use of unlicensed and off-label non-standard formulations that are devoid of relevant scientific data and hence pose a high risk to pediatric patients. The approach to pediatric drug dosing needs to be based on the physiological characteristics of the child and the pharmacokinetic parameters of the drug. This review summarises the current knowledge on developmental changes in absorption, distribution, metabolism, and excretion and combines this knowledge with in vivo and in vitro pharmacokinetic data that are currently available for the ultimate goal of providing infants and children with safe and effective drug therapy and will be made possible by specifically including them in clinical trials. Guidelines formed are intended to be used in clinical practice and to form a basis for more research. Also, the integration of these guidelines, and combining them with pharmacodynamic effects, should be considered and could form a basis for further study.

KEYWORDS: Pediatric, dosage form, pharmacokinetic, pharmacodynamic.

INTRODUCTION
Infants and children are far different from adults in terms of societal, psychosocial, behavioral, and medical perspectives. More than 100 years ago Dr. Abraham Jacobi, the father of American pediatrics, recognized the importance and need for age-appropriate pharmacotherapy when he wrote, "**Pediatrics does not deal with miniature men and women, with reduced doses and the same class of disease in smaller bodies, but... has its independent range and horizon**."[1] It is not enough to simply tailor information available to adults to fit children. In the not-too-distant past, the use of Clark's rule and other formulae assumed children were small or young adults and scaled accordingly.[2]

The pediatric population constitutes a significant portion of the total population. Unlike the overall perception, a pediatric population is a diverse group comprising different subgroups, categorized differently by agencies across the world.

The American Academy of Pediatrics (AAP) considers the pediatric group from the fetus up to the age of 21 (AAP, 1988). The British National Formulary categorizes the separate dosage regimens for neonates (under 1 month of age), children from 1 month to 4 years, and children from 4 years to 10 years (British National Formulary for Children, 2006). Other agencies do not follow this age division. For example, the US FDA classifies neonates into a newborn (1 month of age), infants (1 month–2 years of age), children (2 years–12 years of age), and adolescents (12 years–16 years of age) (US Department of Health and Human Services FDA CDER, 2014).

However, generally accepted subcategories, as per the International Conference on Harmonization of Technical Requirements for the Registration of Pharmaceuticals for Human Use and endorsed by World Health Organization (WHO), are as follows: preterm neonates, full-term newborn infants (birth until 27 days), infants and toddlers – 28 days until 23 months of age, children – 2 years until 11 years of age, and adolescent – 12 years until 16–18 years of age (depends on region) (WHO Technical Report Series No. 970, 2012).

A pediatric population is heterogeneous. Therefore, sometimes, the difference between the dosage of an adolescent and that of a preterm neonate can go up to 100-fold. Similarly, a typical average pediatric dose could be 10% of an adult's dose; however, when compared to a preterm neonate, it can be 10 times the appropriate dose (Grissinger, 2015). Currently, there are very limited medications designed and developed, especially for the pediatric population. The **WHO** in its working document emphasizes on timely development of

medicines for the safe and effective pharmacotherapy of pediatric patients and related information on the proper use of medicine concerning the age, body size, and physiological condition of the child available.

Before the integration of developmental pharmacology into clinical and therapeutic decision-making, numerous approaches to determining pediatric drug doses were recommended (e.g., formulas such as young's rule and Clark's rule). Some of these approaches use discrete age points, whereas others use allometric principles (i.e., those based on relative body size) that generally assume there are predictable, linear relations between mass (e.g., cell mass and body weight) and body-surface area among infants, children, adolescents, and adults.[3]

However, human growth is not a linear process; age-associated changes in body composition and organ function are dynamic and can be discordant during the first decade of life. Thus, simplified dosing approaches are not adequate for individualizing drug doses across the span of childhood.[4] As a result, the use of dosing equations has largely been replaced by adjustment (or normalization) of the drug dose for either body weight or body surface area. Although such guidelines are generally adequate for initiating therapy, they may fall short when it comes to continued or long-term treatment, since maintenance therapy must be individualized based on developmental differences in pharmacokinetics, pharmacodynamics, or both. Thus, the provision of safe and effective drug therapy for children requires a fundamental understanding and integration of the role of ontogeny in the disposition and actions of drugs.

DISCUSSION

In the European Union, the Paediatric Regulation, which was enacted in 2007, resulted in the establishment of the **Paediatric Committee (PDCO).** The main responsibility of the PDCO is to determine the studies that sponsors must conduct on children as part of **Paediatric Investigation Plans (PIPs)**. Because the PIP is rate-limiting among these various legislations, clinical development plans for children will frequently begin with it.

PIPs are the development plans describing the necessary data to be obtained through studies in children that will support the approval of medicine, in the European Union. All applications for new medicines have to include the results of studies as described in an agreed-on PIP unless the medicine is exempt because of a deferral or waiver. This requirement also applies when a sponsor wants to add a new indication, a new dosage form, or a route of administration for a medicine that is already approved. PIPs are rate-limiting because they must be submitted to the PDCO no later than the end of the first phase 1 studies to assess pharmacokinetics in healthy adult subjects or patients.[5] They cannot be submitted after the initiation of pivotal trials, confirmatory, phase 3 trials, or trials conducted in children.

It is important to note that the PIP must be agreed to by the **European Medicines Agency** (EMA) and must be fulfilled by the sponsor unless an amendment is also agreed to by the EMA. Failure to complete the PIP to the satisfaction of the EMA will result in the sponsor being unable to apply for the applicable new pharmaceutical product.[6]

As noted previously, drug development in the United States is governed by the FD&C Act. One of the important milestones is the end of the phase 2 meeting. This meeting is held between the Food and Drug Administration (FDA) staff in the division that is reviewing the ongoing development and the sponsor. The meeting's purpose is to review the safety information that has been gathered in phase 1 and phase 2 studies, to evaluate the phase 3 plan and protocols, to identify additional information necessary to support a marketing application, and to review plans for studies in pediatric subjects.

The **Initial Pediatric Study Plan** (iPSP)[7] describing these studies and/or justification for waivers and deferrals should be discussed with the FDA before the end of phase 2, and the PSP should be submitted within 60 days of the end of the phase 2 meeting. All marketing applications including a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration are required to submit an iPSP.

iPSPs are reviewed by the **Pediatric Review Committee**, which will provide comments to the sponsor and ultimately issue the agreed initial PSP. The **goal** of the **PSP process** is to identify the necessary pediatric studies so that they can be completed before the submission of the new drug application or biologics license application in the case of biological therapeutics. For most sponsors, the iPSP is modeled on the PIP, which is required earlier in development.

GENERAL STUDY CONSIDERATIONS FOR PEDIATRIC SUBJECTS

The age range in a dedicated pediatric pharmacokinetic or pharmacokinetic/pharmacodynamic study should be consistent with the pediatric age range for the intended population of treatment. Clinical trials in pediatric populations are conducted on those individuals who stand to potentially benefit from the treatment. Healthy children participate in studies such as immunization trials against diseases that they might reasonably be expected to contract[8] or postapproval assessment of nutritional supplements.[9]

Reasonably stable children with the target disease participate in clinical pharmacology studies as well as in clinical studies of medications used to treat diseases that occur only in children.[10] Legal regulations and social conventions assert that children lack the autonomy and life experience to judge the risk and benefits of

participating in a clinical trial. Institutional review boards and ethics committees reviewing and approving studies being conducted on children must include adequately trained and experienced clinicians and researchers who can assess the risks and benefits on behalf of the vulnerable pediatric population.

In addition to the consent to participate given by parents or guardians, it is also good practice to provide age-appropriate information about the clinical trial and obtain assent from the potential participants if their maturity and condition allow. Fortunately, as pediatric studies have become a regular part of drug development, expertise is becoming more available. Sponsors have formed internal pediatric councils, among whose members are toxicologists, pathologists, clinical pharmacologists, formulators, assay specialists, statisticians, researchers, and clinicians with expertise in pediatric drug development.

These councils review clinical development plans and study protocols before submission to regulatory authorities to ensure high-quality pediatric development programs that are delivered in a timely fashion while attending to the safety of participants in the trials. In addition to internal pediatric councils, pediatric research networks have been expanded to include sponsors in addition to academic research centers.[11] Research networks improve the efficiency of drug development by providing education and certification for investigators that can be recognized by different sponsors. Through their experience, they can offer direction for improving the trial design,[12] developing and validating standard processes for subject enrollment, dosing, collection of observations, including blood sampling,[13] and information about the natural history of disease, growth, and development. Networks vary in size, diseases, and populations of interest and funding sources. Examples of pediatric research networks are the Children's Oncology Group,[14] the European Network of Paediatric Research at the European Medicines Agency, the Pediatric Trials Network,[15] the Institute for Advanced Clinical Trials for Children, and the Paediatric Trials Network Australia.

PEDIATRIC DOSE

To optimize the **Benefit: Risk Ratio** in trials in patients, investigators try to avoid both ineffective doses and doses higher than required during dose-finding or pharmacokinetic studies and include only doses predicted to achieve concentrations that have been shown in non-clinical studies or simulations to be efficacious and tolerable. When the clearance of a drug can be predicted in children, then the dose required to achieve a target concentration can be calculated. Differences in the volume of distribution must also be considered but are usually of concern only when dosing is intermittent or a particular target concentration must be achieved immediately upon starting treatment. The most common method of determining clearance in pediatric subjects is weight-based allometric scaling.

Clearance is assumed to be a function of weight at three-quarters power.[16] However, because age-related maturation is not included in calculations, allometric scaling is not reliable for young children, especially those younger than 2 years,[17] because of continuing ongoing maturation of metabolic pathways. Segmented allometric models, which implement different exponents for different ages, have been developed to accommodate different age groups[18] and dosage forms such as extended-release tablets that support only limited flexibility in dosing.[19]

Physiologically based pharmacokinetic (PBPK) models may be able to overcome some of the limitations of allometric scaling. PBPK models integrate physiologic information, such as age-specific blood flow, protein concentration, and enzyme and transporter ontogeny with pharmacokinetic parameters such as the percent of the dose eliminated by renal clearance or metabolized by particular pathways and can be used to predict the disposition in children of various levels of maturity.[20,21]

Advances in software and the increased availability of physiological and tissue distribution data have resulted in the more frequent use of PBPK models for drugs in development. Models have been developed for both small molecules and biologics.

Edington and colleagues[22] extended pre-existing PBPK models for acetaminophen, alfentanil, morphine, theophylline, and levofloxacin to include data for children and evaluated the performance of the models in predicting pediatric plasma profiles.

PBPK models are then used to help to design dosing schemes, PK sampling times, and times for other observations in clinical trials in pediatric subjects. For example, sirolimus has not been investigated in children younger than 13 years old, so Emoto and colleagues used PBPK methods to develop a model for sirolimus to make predictions for children aged 1 month to 2 years who were to be enrolled in a phase 2 efficacy and safety trial for the treatment of vascular anomalies.[23] Regardless of the method used to select the doses to be evaluated in protocols, it is a best practice to include a maximum dose to avoid overdosing large or heavy children.

DOSAGE FORMS

In the absence of age-appropriate formulations, medicines that are not licensed for children are used. Such medicines are not properly studied for their effects on children. Considering this, there is a need for formulations developed, which could be suitable for children (WHO Technical Report Series No. 970, 2012).

VARIOUS FACTORS AFFECTING PEDIATRIC DRUG DEVELOPMENT

1. Insufficient background information on drug molecules in the target population.
2. Excipients for pediatric formulations

3. Taste-masking issues
4. Technology requirement
5. Challenges/Risks involved in clinical trials (CTs)
6. Low market size and low profitability
7. Lack of regulatory clarity[24]

The pediatric expert emphasizes the fact that successful drug delivery to pediatric patients can be realized only after overcoming the basic differences between children and adults. The preferred administration route, i.e., oral dosage forms may not always be palatable or available in doses appropriate for children. Thus, dosage forms, such as pills and tablets are often manipulated in ways that are not ideal for delivering safe, effective, and consistent doses. Compounding pharmacists and health workers can help, but their practices may differ, and hence, the results are not always reproducible. Furthermore, these services may not be always available, especially in undeveloped parts of the world. Patients often follow the methods such as dividing doses, crushing and dissolving them in liquids (water, juices, etc.), and administering drugs in quantities that have not been adequately tested (Meyers and Myers, 2016).

In the pediatric pharmacotherapy newsletter, the author reports that optimization of oral drug delivery has been one of the biggest challenges in pediatric pharmacology. For most children over 6 years of age, swallowing solid dosage forms can be taught, and many children remain uncomfortable with it until adolescence. In one study on children, 54% between the age of 6 and 11 years described an inability to swallow a tablet easily (Buck, 2013).

Due to the WHO's efforts, some success is achieved for "tropical" diseases such as malaria and tuberculosis, where pediatric patient-friendly suspension and dispersible dosage forms are becoming available, but the availability of such dosages is still awaited for antiretroviral drugs as HIV/AIDS are the major challenges in these countries (Quique Bassat, 2015). At present, fixed-dose combinations (FDCs) and once-daily solid dosage forms are helping adolescents and older children, but suitable dosage forms are lacking for younger children and infants, which results in poor adherence, viral resistance, and decreased survival of HIV-positive children (Adrienne et al., 2016).

Discussion of dosage forms is an integral part of PIPs, and so each of the following must be described in the PIP document[20,25]: the specific formulation, pharmaceutical form, strength and route of administration for each of the pediatric age groups, potential issues concerning excipients and their predicted exposures at the anticipated dose, administration of doses to the different pediatric age groups, including acceptability, use of administration devices, ability to mix with milk, formula, or food, the precision of the dose delivery and/or accuracy of the dosage form for each of the pediatric age groups, and the anticipated time frame for development of the formulations and dosage forms. Dosage forms used with children must be palatable and must permit flexible dosing to accommodate reasonable precision over the large range of doses that are required.

The relative bioavailability between the different dosage forms must be known so that as children are switched, the required dosing is maintained. Stability information is also required for all dosage forms and understanding of the impact of excursions in temperature, such as when doses are not refrigerated.

Dissolution testing, which is an important metric for the development of oral dosing forms, needs to be evaluated using a relevant dissolution media if the product will be used in very young children whose physiology differs from older children and adults.[26] Beyond oral formulations, differences between adults and children must also be considered.[27] For example, medications that are injected will require concentrations that are neither too potent when it is difficult to accurately administer the very small doses required for premature infants, nor too dilute, which would require large injection volumes that would not be tolerated for subcutaneous injection. There are many different ways of administering medication by aerosol that vary in the effectiveness in delivery as well as the degree of cooperation required of the patient and skill in use by research staff.[28] Drugs administered as eye drops are also challenging for treating conditions in children. Because of the small volume administered, the concentration of active ingredients is high. The eye of a newborn is approximately two-thirds of the adult size and does not reach adult size until age 3 to 4 years. Ocular dosing is not weighted or size-adjusted, so children may receive much higher doses than adults.[29] Protocols and supplementary dose administration instructions need to be clear so that the doses are administered as consistently and accurately as possible.

Monitoring for safety and efficacy in pediatric subjects is incorporated into research protocols in much the same manner as for adults. Baseline assessment takes place before administration of the study drug to verify that subjects are eligible to enroll, do not have any exclusion characteristics, and will be able to cooperate with study assessments.

For the study results to be meaningful, assessments must be age appropriate and capable of detecting safety signals unique to children, such as interference with growth[30] and development. Specific systems may be more (or less) tolerant of drug effects as a result of a combination of differences in physiology and body composition. For example, higher brain penetration of medications in neonates, both human and animal, maybe the result of active transport systems evolved to transport nutrients and other molecules needed for the development of the central nervous system, as well as differences in the volume of distribution related to body

composition, reduced blood plasma protein-binding capacity, and reduced renal flow.[31]

Data analysis methods used for pediatric studies are similar to those used for adult studies. Because of the limited number of samples collected, individual determination of pharmacokinetic parameters for each subject may be only posted hoc estimates based on a population pharmacokinetic model. Naive pooled estimates may also be used to determine pharmacokinetic parameters,[32] although care must be taken to normalize for dose administered and size of the sample of the subjects studied.

Under most circumstances for studies in children, results must be posted within 12 months of the date of final data collection for the prespecified primary outcome measures.[33] European regulations established Article 46 of Regulation (EC) 1901/2006,[34] under which studies, of products that are registered in the European Union, enrolling pediatric subjects must provide a completed clinical study report to the EMA within 6 months of study completion. The requirements apply to all studies with pediatric subjects, even if not included in a PIP. The EMA will in turn make all results available through the EU Clinical Trials Register (www.clinicaltrialsregister.eu).

Publication of study results in a peer-reviewed journal is the final step in making information available to the public. Guidelines[35] have been developed encouraging prompt and balanced reporting of all completed clinical trials, regardless of whether they were positive. Because of the difficulty in enrolling pediatric subjects, these data must be presented and made available to add to the literature. The primary publication is the initial publication of a clinical trial and should be submitted for publication ideally within 12 months (18 months at the latest) of the completion of the clinical trials.[35] Although data are not available specifically for trials of pediatric subjects or clinical pharmacology studies, approximately 90% of studies registered at clinicaltrials.gov have been published.[36]

The expanded scope of clinical trials involving children afforded by the provisions of the Best Pharmaceuticals for Children Act of 2002[37] and an ethical construct for conducting drug research in children that are viewed as permissive (as opposed to restrictive)[38] will facilitate improvements in drug therapy for this age group.

CONCLUSION

The advances in pediatric clinical pharmacology during the past decade stem from an enhanced understanding of the influence of growth and development on the disposition and actions of drugs. The ultimate goal of providing infants and children with safe and effective drug therapy must be kept clearly in sight and will be made possible by specifically including them in clinical trials.

Perhaps more importantly, the advances that are being made to support drug development work in children, including in fragile newborns, can be extended to the study of other vulnerable populations such as pregnant and lactating women. The goal of perfect pediatric posology may indeed be at hand.

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