Abstract
For many years, children have been put at an unnecessary risk through everyday medicines that had not been adequately researched in a pediatric population. The lack of safety, efficacy, evidence-based dosing information, and associated risks for many treatments has led to important pediatric regulations. Pediatric research is now more routinely conducted; however, every study is different and each study design needs to be thoughtfully developed in this vulnerable population. This white paper reviews patient population considerations including the pediatric regulations and guidances, age categorizations, pediatric formulations and administration, dosing considerations, and parent/patient friendly procedures and plans.
Introduction

As a result of legislation in the United States and Europe requiring pediatric research, i.e., Best Pharmaceuticals for Children Act (BPCA), Pediatric Research Equity Act (PREA), and the Paediatric Regulation, pharmaceutical companies have substantially increased the number of pediatric research studies they conduct. The progress is certainly positive and further emphasizes the critical need for appropriate development and evaluation of medications in children, thus limiting off-label use, unproven extrapolation from adult studies, and increased risk of adverse events.

The industry recognizes the importance of ensuring the safety and well-being of children involved in research studies through appropriately designed, well-controlled studies that take into consideration the ethical rights and needs of this vulnerable population. When designing pediatric studies, one must carefully consider challenges that are specific to the age ranges of the children. A critical first step is to ensure that the protocol is scientifically rigorous while still parent/child friendly. It is important to strike the fine balance between:

- Regulatory requested study designs and realistic, executable trials
- Proper statistical powering of studies versus practical recruitment potential
- Obtaining quality data versus exposing as few children as possible to both investigational products and invasive procedures
- Study goals versus the protections provided by the IRB/EC

The following paper provides useful information to consider when developing studies in pediatric populations.

Pediatric Regulations and Guidances

Regulatory agencies and medical bodies have both worked to provide a framework to support the development and conduct of pediatric research studies through regulations (i.e. the rules to be followed) and guidance documents (i.e. the opinions on how to follow the rules). Before beginning any pediatric program it is important to understand and comply with this framework.

The Food and Drug Administration (FDA) website (www.fda.gov) provides an excellent library of material on the Agency's current understanding of the rules governing pediatric clinical trials. Useful insights into pediatric protocols can be found by reading the FDA reviews of the drug applications for pediatric indications. This is especially true for the reviews of applications that the Agency finds to be inadequate.

In addition, the European Medicines Agency (EMA) website (www.ema.europa.eu) provides details on the Paediatric Regulation's objective to improve the health of children without subjecting children to unnecessary trials or delaying the authorization of medicinal products for use in adults. The Paediatric Regulation established the Paediatric Committee (PDCO), which is responsible for coordinating the Agency's work on medicines for children. This committee determines which studies and protocols are required as part of pediatric investigation plans (PIPs). All approved PIPs can be found on their website.

The International Conference on Harmonisation (ICH) E11 Guideline addresses the conduct of clinical trials in pediatric populations and supports timely pediatric product development. This document outlines critical issues relating to pediatric drug development and provides approaches for safe and ethical research in the pediatric population.

In addition to these recognized regulations and guidances, medical organizations such as the American Academy of Pediatrics will sometimes provide their own recommendations, which often provide supplemental information on protocol design.

Research is Making a Difference

Since the enactment of Food and Drug Administration Amendments Act (FDAAA) on September 27, 2007, 360 pediatric studies have been completed on 153 products. These studies included more than 165,000 children and have led to:

- 130 labeling changes that expanded the age to include pediatric age groups not previously included
- Eight changes specific to dosing changes or adjustments
- 30 changes with new or enhanced pediatric safety information
- 37 changes where safety or efficacy was not established in a pediatric population
- One change that included a box warning with pediatric information

Source: FDA website
Data includes information through 2011

Pediatric Resources

FDA
- 45 CFR 46 Subpart D, Additional Protections for Children Involved as Subjects in Research
- 21 CFR 50 Subpart D, Additional Safeguards for Children in Clinical Investigations
- General Considerations for Pediatric Pharamacokinetic Studies for Drugs and Biological Products
- Qualifying for Pediatric Exclusivity under Section 505A of the Federal Food, Drug, and Cosmetic Act
- Guideline for Industry: How to Comply with the Pediatric Research Equity Act

EMA
- Guideline (2008/C 243/01)

ICH
- Guidance for Industry: E11 Clinical Investigation of Medicinal Products in the Pediatric Population

American Academy of Pediatrics
- Guidelines for the Ethical Conduct of Studies to Evaluate Drugs in Pediatric Populations (2010)
In addition, there are specialty guidance documents for specific disease categories and drug products.

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DEVELOPING PEDIATRIC STUDIES:
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Developmental Differences

Just as children differ from adults, the various pediatric age groups differ from each other and are considered separate labeling indications. Body compositions are different at the various ages.

**Pre-term newborns** present special challenges because of unique patho-physiology and responses to therapy. Important considerations include low birth weight, immaturity of renal and hepatic clearance mechanisms, protein binding and displacement issues, unique neonatal diseases, respiratory complications and underdeveloped organs. The amount of blood that can be safely drawn from a pre-term baby is minimal.

**Newborns** have rapidly developing organs and have an immature blood brain barrier. Oral absorption is unpredictable in this subgroup.

**Infants & Toddlers** continue to present challenges due to their rapid growth. In addition, drug compliance can be difficult in these first three groups and special formulations are often needed.

**Children** can be difficult patients for doctors – many in this age group have fear of doctors/needles. From a medical perspective, they require monitoring of development including weight gain, skeletal growth and cognitive development.

**Adolescents** have a lot more independence and may be non-compliant with study directions. Privacy can be an issue, and they can be uncomfortable with discussing pregnancy tests and birth control. They need to be monitored for adverse effects associated with reproductive development and hormonal changes may influence the results of studies.

Age Categories

Importantly, studies need to be conducted in each age group in which an investigational product will be used or the indication is relevant and all other age groups should be excluded (as negotiated with the agencies) to ensure children are not subjected to trials unnecessarily. Due to the overlap and individual variability in development (physical, cognitive and psychosocial) age categorization is not finite. One possible categorization scheme, which has been proposed by the ICH and has been accepted by the FDA, is shown below.

The decision on which age ranges are appropriate for inclusion in a particular pediatric study are twofold: (1) for which age group(s) is there sufficient safety data to permit the use of the study drug at therapeutic doses, and (2) in which age ranges do children suffer from the malady being studied and therefore potential exposure to the study drug is probable. It is important to understand the natural history of the disease in question and to be able to articulate why the investigational product would be of potential benefit to patients in the selected age groups. Alternatively, it is important to be able to articulate why and when a drug would not be of benefit to patients in selected age groups and to negotiate a waiver with the applicable agency.

Ideally, age categories would be rationally defined based upon the patients’ development, disease or condition under study, and the investigational drug, but because a detailed understanding of the effect of age often will not be obtained until after the study is completed, it may be necessary to design a study using the suggested ranges shown. However, when appropriate, because of variability in development, as opposed to a strictly age-based system of age categorization, it may prove useful when grouping pediatric patients to take developmental biology and pharmacology into consideration. As a simplistic example, a study assessing the safety of a new birth-control pill would be inappropriate in girls prior to menarche regardless of the chronological age. Thus, the FDA has on occasion suggested that instead of classifying adolescents as being greater than a particular age, this age range be defined as beginning with Stage 3 on the Tanner physical-development scale.
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Well-defined age groups allow the reviewer to assess, for example, the safety of the study drug in infants compared to adolescents. For example, kidney function increases rapidly with age, which may mean that toxic breakdown products may potentially build more quickly in infants compared to adolescents. Grouping infants with adolescent patients for safety assessment might dilute or mask serious safety issues.

In the end, age categorization facilitates the analysis of the study results and guides evidence based labeling of the drug in the pediatric population.

Pediatric Formulations and Administration

Children—40% of the world’s population—are treated with suboptimal dosing and many underdeveloped countries lack access to new medicines with stable shelf formulations.

Often adult formulations are not appropriate for children and the time and cost considerations for the development, manufacturing, stability and packaging of pediatric formulations are significant. As such it is important to consider the suitable formulations for all relevant pediatric subpopulations very early in the pediatric plan development.

Determining the best pediatric routes of administration, whether it be oral (as a liquid, chewable, dissolvable, mini-tablet, etc.), transdermal, injectable, via inhaler, suppository, etc., requires substantial preclinical work, and this critical timeline is often underestimated. Factors that need to be taken into account include:

- Age
- Physical Development
- Illness
- Treatment Duration
- Dosage
- Dosing Frequency
- Route of Administration

Pediatric patients are dynamic with respect to drug disposition due to developmental changes in body composition, drug metabolism, and organ function. The typical complex solid dosage form is not engineered with consideration of pediatric GI physiology and oral liquids and chewable/dissolving dosage formulations can be limiting due to palatability. Frequency of dosing in children can be a particular problem with school-age children. Additionally, it is important to ensure safe and precise administration with all pediatric formulations. These practical considerations make the determinations for formulation much more challenging in pediatric trial design.

The formulation of the drug can play a significant role in the acceptability of a study. Children will refuse an unpleasant formulation and poor compliance increases the risk of therapeutic failure. Compliance can be fostered by delivering a formulation with an acceptable taste. Administration of drug combined with food/drinks should also improve acceptability, but compatibility, stability and bioavailability (food effect) will then also need to be investigated.
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While oral liquids may seem the most appropriate for babies and very young children, this form is the most challenging because of taste and stability. Liquids typically require larger amounts of excipients which are limited in neonates and infants due to immature renal and hepatic functions. Solid dosage forms are more stable and have more taste masking techniques available but have less flexibility in terms of dosing.

While compliance will obviously improve if a formulation is better tasting, the importance of child-proofing then becomes more important. A pleasant tasting cherry or bubblegum flavored liquid may make the study more easily accepted by both parent and child, but it may also increase the risk of accidental overdosing by the patients or curious siblings.

Additionally, when assessing the acceptability by parents and patients, sponsors often overlook the storage requirement of the drug. Drugs that require refrigeration present logistical issues during the school day, during vacations, etc., and this should be further considered in final plans for formulation development.

Dosing Considerations

Currently available data for the pediatric population can be used to establish the initial therapeutic dose for the pediatric testing. In cases in which such data is lacking, the FDA recommends that initial doses, based on mg/kg of body weight or mg/m2 of body surface area, be extrapolated from adult doses, provided that the pharmacokinetics and pharmacodynamic properties of the drug are well known. This extrapolation will require that the pharmacokinetic characterization in the adult population be combined with a firm grasp of the physiological development of the pediatric populations, in particular the maturation of the metabolic processes, to ensure that the initial dose estimate is safe and reasonably likely to be efficacious. Clinical observations and real time assay of drug concentrations provide the strong basis for dose adjustment, if required, and dosing considerations can be more comprehensively determined by the use of AUC exposure rather than administered dose. Population PK studies can provide comprehensive information on the effects of age, weight, and sex difference in children leading to better dosing recommendations.

As safety is of paramount importance for initial testing, it is vital to consider doses that are only a fraction of the adult dose when the dose-response effect of the drug is either unestablished, nonlinear, or likely to be dependent upon the physiological development of the patient. Knowledge of most common dose limiting toxicities observed in adults may also provide additional safety when estimating an appropriate dosage in children. This is especially the case in younger children whose ability to metabolize the drug may vary greatly between individuals of the same age, as well as change significantly over time.

It may be necessary to first establish therapeutic dosage for adolescents before considering use in younger patients. Such an approach may require multiple studies and is a common request from regulatory agencies and ethics review boards.

Patient/Parent Friendly Procedures and Plans

Many aspects of pediatric clinical trial design must be approached proactively to ensure successful and safe enrollment of children. The trial design has to be acceptable to the referring pediatrician, the pediatrician investigator, the parents (or other caregiver) and to the child. The protocol should be rigorously evaluated to be certain that each study visit/procedure is truly needed to ensure both patient safety and scientific quality. Emphasis should be placed on limiting the intensity and frequency of study assessments, especially invasive and painful procedures as much as possible. Additionally studies should be designed to ensure that blood sample volume does not exceed institutional or national standards.
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Minimize Pain and Distress

It is important to accommodate the young population where possible and minimize intensity and frequency of the study assessments. Examples include:

- Limit invasive procedure as much as possible
- Limit number and volume of blood draws – coincide the collection of protocol-specified blood samples with routine clinical samples
- Provide EMLA numbing cream
- Use smallest possible needle size such as butterfly
- Provide pediatric tubes to hospitals/clinics that routinely and only use larger tubes appropriate for adults

The protocol should clearly specify the procedure, the length of the procedure, and describe any discomfort that the procedure may cause. The description of all study procedures, including the pre- and post-procedure requirements, must be described in the study protocol, parental permission/consent and pediatric assent form.

Remembering that child equals family is important in the planning and logistics for pediatric studies. Parents need to be able to coordinate travel and study commitments around work, school and extracurricular activities for both the patient and siblings. The timing and frequency of study visits as well as the frequency of dosing are critical.

Increased access to health care providers with in depth understanding of the underlying malady is extremely supportive and motivational for families. Additionally, educating parents and the child about the goals, benefits, and risks of the study are important and empower them to make best choices for study inclusion and understanding their commitment and responsibilities for the study. Attention to these nuances will support the most successful studies and will ensure compliance and quality results.

Summary

Regulations and cultural demands for evidence-based pediatric drug development continue to increase and, as such, most companies in the biopharmaceutical industry will be impacted in some manner. An important part of this emphasis is education and the thoughtful application of the ethics and science important for research in children. As the saying goes, children are not little adults, and special considerations for this dynamic and vulnerable patient population must be taken into account in the development of pediatric studies. Knowledge of the regulatory requirements as well as characteristics unique to the age groups being studied are critical to the feasibility and success of any pediatric trial. Beyond the physiological differences, it is necessary to consider drug formulations and dosing for safe and effective pediatric drug studies. Operational logistics should be incorporated into the study design to account for families and the real-life challenges important to enrollment, compliance, and the study's overall quality. While every study is unique, this white paper has highlighted population specific considerations important for the development of pediatric drug studies.

In Part 2, the discussion will continue with a focus on the biostatistical and pharmacokinetic considerations for pediatric studies.

About Premier Research

Premier Research is a leading global contract research organization (CRO) serving biotech, pharmaceutical, and medical device corporations. Its services include clinical research and regulatory outsourcing in the areas of analgesia; neurology; infectious, cardiovascular, and respiratory disease; dermatology; and oncology. The company also has a wealth of experience in medical device and pediatric research.

In fact, Premier Research specializes in helping biotech and pharmaceutical corporations comply with PREA (Pediatric Research Equity Act of 2003) in the U.S. and, in Europe, with the European Pediatric Regulation, which requires biopharma companies to submit a Pediatric Investigation Plan, or PIP. Premier Research's clinical research experts are recognized as among the authorities in the industry.

Premier Research has 21 offices (seven in North America, 14 in Europe) and operates in 23 countries. It employs 1,000 clinical professionals dedicated first and foremost to fulfilling each client's requirements in a timely, accurate, and cost-effective manner. This includes a strong international network of monitors and project management professionals combined with regulatory, data management, statistical, scientific, and medical experts, and staff at its well-established network of dedicated clinical sites.
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