The What, Why, & When of Pediatric Extrapolation: Minimizing the Burden of Clinical Trials on Children to Accelerate Pediatric Drug Development

Highlights:

- Pediatric development is now mandated for all new medicines that do not have a class waiver or orphan disease designation in the US.
- The FDA and EMA have established Pediatric Extrapolation Guidances that permit the extrapolation of adult efficacy data to children through the implementation of smaller focused pharmacokinetic (PK) and safety trials.
- Advances in extrapolation coupled with modeling and simulation hold huge promise for drug developers to efficiently bring important medicines to children.

Introduction

Pediatric development is now mandated for all new medicines that do not have a class waiver or orphan disease designation in the US. Comparable, if not more rigorous, pediatric requirements are also in effect in the EU regardless of orphan disease status. From the Best Pharmaceutical for Children Act (BPCA), to the Pediatric Research Equity Act (PREA) and the Food and Drug Administration Safety and Innovation Act (FDASIA) in the U.S. to the Pediatric Regulation of 2006 in Europe--drug developers face increasing requirements to develop high-quality, age appropriate medicines for pediatrics.

These regulations were implemented to address the growing concern that the vast majority of drugs (>70% for children and >90% for neonates) were historically being prescribed off-label and in many cases had not been formally evaluated for safety and efficacy in children. This problem was also exacerbated by the fact that drugs designed for adults often required ad hoc extemporaneous formulation e.g. by crushing tablets and introducing the divided dose into food substances like apple sauce.

The pediatric regulations that are now in place in the U.S. and EU were introduced to a) reduce the off-label use of drugs in children, b) provide a structure for the proper evaluation of the safety and efficacy of a drug in pediatric patients, and c) promote the development and availability of age appropriate formulations for children.

One of the major challenges in conducting clinical trials in children, especially in rare and orphan diseases, is the limited availability of patients and reluctance of many parents and caregivers to enroll their child in a trial with an experimental therapy. Realizing these challenges and looking for innovative ways to minimize the number of children that need to participate in a clinical trial, the FDA and EMA have established the concept of pediatric extrapolation to facilitate the extrapolation of adult efficacy data to children, provided that certain conditions can be met.

What Is Pediatric Extrapolation?

Pediatric extrapolation is an approach that the EMA and FDA are encouraging sponsors to adopt to minimize the number of children that are required to participate in clinical trials. It involves leveraging available efficacy data generated with a given drug in adults to inform pediatric clinical trials and in certain instances circumvent the need to conduct large scale, statistically powered, Phase III efficacy trials in children.

In order to implement an extrapolation approach, certain requirements first need to be met:

1. the disease/condition is the same in adults and children
2. the response to treatment is anticipated to be comparable, and
3. that an exposure response (PK/PD) relationship be demonstrable from the adult data.

If these conditions can be satisfied, then the guidances permit the extrapolation of adult efficacy data to children of different ages after an appropriate dose adjustment for age and maturation has been made.

In order to be able to utilize the adult efficacy data, a PK study that demonstrates equivalent systemic exposure to adults is typically required. This data, together with the development of an adequate safety database across different pediatric age groups, can then be used to support pediatric labeling without having to conduct large scale, statistically powered trials.

Why Is It Important?

Traditionally, pediatric clinical trials are lengthy and expansive, requiring a large number of patients to be enrolled. A conventional development pathway without extrapolation might require two Phase II dose-ranging studies in children and perhaps one to two large Phase III scale trials, involving hundreds of patients, taking several years to enroll subjects and gain drug approval.

Efficiencies in trial design from a study using an extrapolation framework may include streamlined timelines, a reduction in the need for subject by one-third or more, and/or significantly reduced costs for the pediatric clinical trial. In some cases, a single pharmacokinetic study to establish systemic exposure in children and open label safety database may be sufficient to support product labelling (i.e. full extrapolation). In other instances (e.g. where the response to treatment in children may be different to adults, or there are some uncertainties around the PK/PD relationship), additional confirmatory measures to support efficacy, such as the inclusion of a biomarker or other measures of clinical benefit, may be needed to support a partial extrapolation approach. In either scenario, the implementation of an extrapolation approach can lead to a significant reduction in the number of patients, time, and cost required to demonstrate clinical benefit in children for product labelling.

Today, both the Paediatric Investigation Plan (PIP) in the EMA and Pediatric Study Plan (PSP) in the U.S., contain sections on extrapolation. These incorporate an assessment of what is feasible based on the current state of existing adult knowledge on the drug/disease, PK/PD information established in adults, response to treatment, and necessary background work need to implement such an approach.

While many companies may have opted not to consider extrapolation in the past, instead making commitments (in PIPs and PSPs) to do full scale pediatric Phase II or Phase III initial dose finding studies, the tide is changing. While certainly the former can be acceptable, it might not always be the optimal way to go. Drug developers might later learn, upon trying to operationalize these large studies, that the cost, time, and commitment make them insurmountable. As a result, they might have to renegotiate an amendment to the pediatric plan, requiring additional time and cost.

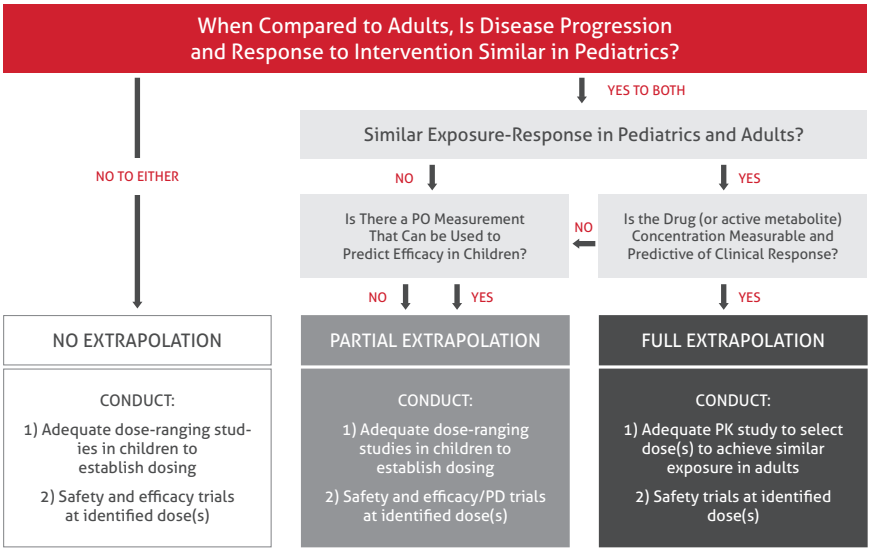
Complete, Versus Partial, Versus No Extrapolation?

In looking at the feasibility of data a sponsor currently has, a case could be made for partial or full extrapolation to reduce the size, scope, and cost of the pediatric clinical timeline. While subjective and based on a number of factors, a full or partial extrapolation approach can compress pediatric clinical trial timelines by months or even years. It may also provide the basis for an approval in situations where traditional Phase II-III studies may never be in position to fully complete enrollment in a timely manner due to the lack of available patients and competing trials. This is particularly the case for pediatric rare and orphan diseases that still must comply with EU pediatric regulations.

The U.S. Perspective

The U.S. pediatric extrapolation guideline may be the easiest to understand as it defines three categories including, full, partial, and no extrapolation:

The FDA Extrapolation Decision Tree



1 **Full Extrapolation:** Pictured on the far right-hand side of the decision tree, full extrapolation, is a best case scenario for sponsors seeking to develop drugs for pediatric use (it applies to approximately 15-20% of drugs). This type of extrapolation enables the sponsor to fully leverage adult efficacy data to develop a labeling claim without having to do additional clinical studies.

   The sponsor is required to determine appropriate dosage across pediatric age ranges for the same circulating levels as seen in adults where the efficacy, exposure matching is demonstrated. A pharmacokinetics (PK) study to match that same peak level of exposure shown in adults in children, is necessary. This study can help to determine the extent of exposure to the drug in plasma for a given dose level based on blood sampling over a period of time. Additionally, safety data, at the identified dose, is required. A reasonable size safety database might include 100-150 pediatric subjects, or even less in rare and orphan trials.

2 **No Extrapolation:** On the opposite end of the decision tree, where another 15-20% of drugs will fall, is no extrapolation. Clinical trials that fall into this category most often involve pediatric-only diseases that do not exist in adults and, therefore, have no data from which to extrapolate. An example is retinopathy of prematurity, which can lead to blindness in pre-term infants. As this is a pediatric-only disease, a full development plan is necessary.

   Under these circumstances the FDA guidance recommends pharmacokinetic data/ dose ranging studies and one or two adequate, well-controlled efficacy and safety trials with children in studies involving no extrapolation.

3 **Partial Extrapolation:** The majority of pediatric clinical trials, about 60%, will fall in the middle category with partial extrapolation. In these trials, efficacy data can be extrapolated from adult studies using PK/exposure matching principles (as in the case of full extrapolation) but sponsors may need to get additional efficacy or biomarker data in the pediatric population to verify the response and treatment benefit.

For this level of extrapolation, adequate dose ranging studies and safety and efficacy trials are generally needed. There are various degrees of requirements for them, based on each trial's specific circumstances, however partial extrapolation e.g. in the form of a single open-label, non-statistically powered PK/Safety study with an associated measure of PD, may be all that is required for labelling.

With the FDA, pediatric safety is not extrapolated. In some cases, the sponsor may be able to utilize safety from a similar pediatric indication in a similar population. However, while other sources of safety may inform the development of pediatric safety programs, safety needs to be assessed in the pediatric population for each study.

The EU Perspective

While the EU follows similar requirements for extrapolation, the EMA views it more as a continuum that can be applied from full extrapolation to no extrapolation, versus falling into specific discreet categories. The EMA also want sponsors to identify and address areas of uncertainty in the data approach as part of the extrapolation plan and analysis.

Common Principles

The level of extrapolation is determined broadly regardless of application in the U.S. or EU. Extrapolation is based on proving three defining principles. The sponsor needs to show the following to obtain acceptance of extrapolation:

1. **The disease in adults and children is the same disease.**
   Regulatory authorities want the sponsor to show that the data they are gathering around adults with a specific disease is applicable to children with that disease (i.e., the data will be relevant and can extrapolate to pediatric populations). For instance, an infection will likely involve the same microorganism in both adults and children. Conversely, certain cancers in adults may have the same classification in children, while the mutations and disease may differ. In the latter, data gathered in adults may not be directly applicable to children.
2. **The expected response to treatment will be equivalent in adults and children.**
   The sponsor needs to demonstrate that the response to therapy is likely to be same. If the sponsor cannot demonstrate this, it may be asked to provide additional research in the pediatric population. While demonstrating this adult/child relationship may be fairly easy in some diseases, such as with the infection/antibiotic example above, children may respond more effectively or poorly to treatments than adults in other cases.
3. **The PKPD relationship – or mathematical relationship between exposure of drug in plasma and the time course to response to treatment – can be demonstrated in adults.**
   Sponsors must show that they mechanistically understand the relationship between the dose of a given drug, the exposure generated by it, and its relationship to response & treatment. If an exposure-response (or PK/PD relationship) can be demonstrated in adults and the other conditions described above can be fulfilled, then the adult efficacy data may be extrapolated to children. This is done by appropriately scaling the dose so that drug exposure in children matches the exposure in adults i.e. that pediatric "exposure-matching" can be achieved.

Is Pediatric Extrapolation Feasible for Your Drug?

To determine if pediatric extrapolation is a feasible option for your pediatric program, sponsors should undertake an assessment of a) the nature of the disease or condition in the adult and pediatric patient populations, b) if a PK/PD relationship exists or can be established from the available clinical data, and c) if the response to treatment is likely to be comparable in adults and children. If all or some of these prerequisites can be established, then a full or partial extrapolation strategy may be possible.

Timing to make these assessments is generally triggered by pediatric planning requirements. In the EU, for instance, the PIP has to be developed earlier, prior to the end of the Phase I study. In the U.S., the iPSP must be submitted 60 days after the end of the Phase II meeting.

Companies planning to conduct trials in the EU must formally engage with EMA and PDCO to get plans in place sooner, often even before full data is available for adults. Therefore, the PIP is often based on acquisition of future data, versus in U.S. where adult clinical PK and efficacy data may be available for analysis to assist in pediatric planning.

Feasibility Analysis – What to Look For

While the sources of data available to assess extrapolation have not changed significantly over the years, how organizations can assess them has. Techniques for modeling and simulating PK/PD, clinical trials, and disease states have advanced significantly.

Three key tools in assessing extrapolation include:

- **Pharmacokinetic/Pharmacodynamic (PK/PD) Modeling**
  PK/PD (or exposure-response) modeling is foundational for pediatric extrapolation, offering critical insights into the relationships between dose, systemic exposure and response to treatment. Sponsors should seek to partner with experts in this space with deep therapeutic area knowledge and PK/PD modeling & simulation experience with a vast array of small molecules & biologic therapies.

- **Physiologically Based PK (PBPK) Modeling & Whole-Body Simulation Platforms**
  Advanced approaches such as whole-body modeling or Physiologically-Based PK (PBPK) modeling are used to predict and select pediatric dosing regimens for use in clinical trials. PBPK modeling is used to predict the best doses and dosing regimens to be evaluated in pediatric patients to achieve exposure matching to adults. It accounts for differences in anatomy, physiology, and body composition between adults and children as well as differences in age, bodyweight, gender, race, organ function, and gene expression due to different stages of maturation. This state-of-the-art predictive modeling is the method of choice to address the regulatory, clinical, and scientific needs associated with pediatric dose prediction.

- **Population PK (POP PK) and sparse sampling**
  Extensive blood sampling is frequently employed to collect PK data in adult clinical trials. However, this can be very challenging and often impractical to implement in a pediatric trial setting for exposure-matching purposes. To minimize the total blood volume and the number of invasive blood sampling procedures it is often necessary to implement a sparse blood sampling strategy for PK testing. This can be achieved through the use of Population PK (or PopPK) methodologies. PopPK and sparse sampling allows researchers to determine: 1) the minimum blood samples needed, and 2) the best time to collect samples following dosing to obtain high quality data for pediatric exposure-matching. This approach can also provide valuable information on how drug clearance is influenced by factors such as age, gender, race, bodyweight, body surface area, hepatic and renal function, and concomitant mediations, etc. to inform product labelling and use

Conclusion

Pediatric extrapolation enables drug developers to leverage disease and drug data from adult populations to guide, inform, and in some cases reduce or replace the need for conventional large-scale pediatric trials. It is a growing strategy, that is being actively developed and refined by both the FDA and EMA, which has helped to maximize the use of existing data and increase the efficiency of pediatric clinical trials while maintaining their safety.

Advances in extrapolation with modeling and simulation hold huge promise for drug developers to bring important medicines to young patients at optimal doses, sooner. These advanced tools are additionally helping drug developers to reduce the need for extensive testing on these precious patient populations.

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O - Cosmetic: 1%

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