PAEDIATRIC PRODUCTS IN PQT - MEDICINES

The development of paediatric formulations for essential medicines has been recognized as a critical step for successful healthcare delivery. However, because the majority of clinical studies conducted during pharmaceutical product development are conducted in adult subjects, the development of paediatric formulations and dosing regimens is not straightforward. In fact, their development typically requires the use of special design considerations for paediatric clinical trials and the use of additional tools to supplement the available clinical data. Indeed, because of the difficulties associated with collecting data from the paediatric population due to ethical and feasibility-related issues, much of the work related to the development of paediatric dosing regimens and subsequently, selection of strengths for paediatric products, relies heavily on additional design tools such as paediatric extrapolation, and modelling and simulation. The application of these tools exploits the existing knowledge in the adult and paediatric populations as well as knowledge regarding the characteristics of the active pharmaceutical ingredient (API), the disease pathophysiology, and existing nonclinical data.

The International Council on Harmonisation (ICH) guideline *Addendum to ICH E11: Clinical investigation of medicinal products in the paediatric population* defines 'paediatric extrapolation' as "an approach to providing evidence in support of effective and safe use of drugs in the pediatric population when it can be assumed that the course of the disease and the expected response to a medicinal product would be sufficiently similar in the pediatric and reference (adult or other pediatric) population."[1] This guideline provides a good discussion of what data should be considered for the purposes of extrapolation to develop a strategy for the safe and efficacious use of an API in the pediatric population.

The rapid advancements in the areas of clinical pharmacology and quantitative modelling and simulation techniques since the issuance of the original ICH E11 guideline in 2000, has resulted in modelling and simulation becoming powerful tools for addressing knowledge gaps when developing pediatric dosing strategies. These take into account the non-linear effects of body size and maturation. Considerations for the use of modelling and simulation for the development of pediatric dosing regimens and strengths are also discussed in the recent Addendum to ICH E11[1]. The ICH E11A working group is currently developing a more detailed guidance on how pediatric extrapolation can be used in successful pediatric product development.[2] In the HIV field, WHO and UNITAID have produced a well-documented toolkit for research and development of pediatric antiretroviral drugs and formulations.[3] There has been recent literature on clinical trial designs that will maximize output of useful paediatric evidence.[4] Together these tools can be used to provide direction during the identification of paediatric dosing regimens for medicines and subsequently the selection of paediatric strengths for the necessary products. However, it is important to note that additional clinical data may be necessary in some cases to support the dosing/strength selections made based on the available data.

Identification of a paediatric strength for a product on the WHO Prequalification Team – Medicines' (PQT/MED) Invitation for Expression of Interest (EOI) does not necessarily confirm that all necessary clinical data for that paediatric product has been collected and assessed. On the other hand, in other cases, applications for prequalification of a paediatric product may only require submission of a bioequivalence study comparing the proposed product to the PQT/MED-identified acceptable comparator product.

In vivo bioequivalence studies are generally conducted in healthy adult volunteers, except in those cases where the drug carries safety concerns of such significance to make the use of healthy volunteers unethical. In such rare cases patients need to be employed. Healthy volunteers are considered to be a predictive and sensitive surrogate model for establishing that two products perform in an equivalent fashion, i.e., for demonstrating bioequivalence and to detect bioavailability differences between formulations in the different patient populations (e.g., elderly patients, patients with renal or hepatic impairment, females, different races, etc.). Similarly, generally the demonstration of bioequivalence obtained in adult healthy volunteers can be extrapolated to paediatric patients since, presently, there is no evidence suggesting that those products that have been shown to be bioequivalent in adult healthy volunteers are not bioequivalent in paediatric patients. Therefore, if a target dose is identified for paediatric administration and a paediatric strength product is desired to deliver that dose, in many cases the paediatric strength can be tested in a bioequivalence study in healthy adult subjects where multiple units of the proposed paediatric product are compared to an equivalent dose of the higher strength adult product. Once it is confirmed in a bioequivalence study that the proposed paediatric strength performs in a dose proportional fashion to the existing adult strength, e.g., 5 x 100 mg (the paediatric strength) is equivalent to 1 x 500 mg (the adult strength), it can then be used to deliver the desired lower dose to the paediatric population.

When conducting bioequivalence studies, it is essential to administer the test and the comparator product according to their corresponding instructions for use. In those cases where the test and the comparator product are different dosage forms with different methods of administration (e.g., a tablet that should be taken with a glass of water, an orodispersible tablet that can be taken without water, or a dispersible tablet to be dispersed in 10 mL of water) the bioequivalence study should be conducted employing the intended method of administration of each product. It is considered incorrect to standardise the volume of liquid in all these cases (e.g., administering a glass of water after the intake of the orodispersible tablet, a syrup, or an oral suspension, or rinsing the container where a dispersible tablet has been suspended with the remaining liquid of a glass of water) because this standardisation does not occur in real life conditions. The total volume of water employed during administration of a pediatric dispersible tablet should not exceed 50 mL.

It is recommended that applicants interested in submitting an application for a paediatric product on a PQT/MED EOI consult with PQT/MED to confirm the study requirements for that product, i.e., whether a single bioequivalence study is sufficient or additional data requirements are needed, e.g., clinical data collected from a paediatric subgroup(s).

1. ICH Harmonised Guideline Addendum to ICH E11: Clinical investigation of medicinal products in the paediatric population, 18 August 2017 at
   https://database.ich.org/sites/default/files/E11_R1_Addendum.pdf

2. ICH Draft Guideline E11A: Paediatric Extrapolation 4 April 2022 at
   https://database.ich.org/sites/default/files/ICH_E11A_Document_Step2_Guideline_2022_0404_0.pdf

3. WHO & UNITAID
   Toolkit for research and development of paediatric antiretroviral drugs and formulations
   https://iris.who.int/bitstream/handle/10665/273151/9789241514361-eng.pdf?sequence=1

4. Ford D et al,
   Optimizing Clinical Trial Design to Maximize Evidence Generation in Paediatric HIV
   JAIDS Journal of Acquired Immune Deficiency Syndromes: August 15, 2018 - Volume 78 - Issue - p S40–S48
   https://journals.lww.com/jaids/fulltext/2018/08151/Optimizing_Clinical_Trial_Design_to_Maximize.8.aspx