PK/PD Modelling as a Critical Tool Behind the Regulatory Strategy for an Agile and Cost-Effective Pediatric Development Plan (PIP/PSP)

An Example of Weight Management

Regulatory authorities generally require a Pediatric Development Plan, referred to as Pediatric Investigation Plan (PIP) in the European Union (EU) or Pediatric Study Plan (PSP) in the United States (US), for a new drug to be approved. Depending on the condition and type of product, clinical data in children and adolescents may be needed for the approval of a new medicinal product.

However, in many cases, clinical studies in children can be waived or reduced in number of participants, and data from adults can be leveraged to support the treatment of children.

Our regulatory strategy team and experts in Model Informed Drug Development (MIDD) gather to design the best possible approach for an agile and cost-effective Pediatric Development Plan (PIP/PSP).

The following scenario illustrates a potential approach to supporting our clients' needs.

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Project Overview

A biotech company has successfully completed a Phase II study evaluating the efficacy and safety of a new product for weight management, and a Phase III study is planned involving multiple sites across US and EU. The studies completed include adult population only. However, a Pediatric Development Plan (PIP/PSP) is required.

This company engages our regulatory strategy team who, in collaboration with our MIDD experts, design a PIP, in which the main measures include: developing pharmacokinetic (PK) and exposure-response (ER) models to determine and justify the doses to treat adolescents and children, treating a limited number of pediatric patients in an ongoing Phase III study.

Background

The development of new medicines for weight management typically requires clinical data from several thousand patients. The US Food and Drug Administration (FDA) recommends a safety population of 3,000 subjects randomized to the investigational drug and no fewer than 1,500 subjects randomized to placebo for at least one year. Beyond this, a PIP/PSP should be developed to support the treatment of pediatric patients, which should generally include the development of a pediatric formulation, as well as nonclinical and/or clinical aspects. A waiver of clinical studies for a specific age range may be granted. Otherwise, clinical studies in pediatric populations may be needed, which could be deferred post-approval of the product in adults.

Some of the weight management products on the market are already approved for the treatment of adolescents ≥ 12 years of age. While all the approved products have waivers for children < 6 years of age, data to support the treatment of children aged 6 to 12 years is still expected by the regulatory authorities. Indeed, prior to market approval, all the products currently approved for weight management have committed to perform clinical trials in children aged 6 to 12 years.

Key Challenges

- The weight management market is extensive; however, it is characterized by significant competition, including multiple approved products and a robust pipeline of treatments, with several candidates having advanced to Phase III. Within this highly competitive landscape, it is critical to reach the market as soon as possible.
- While children may not be the most relevant target population for a weight management indication, approval in adults is only possible when a PIP/PSP is agreed upon with the regulatory authorities. Clinical studies in children can be deferred post-approval, but a commitment to compile evidence to assure an efficacious and safe treatment in children needs to be in place before approval.
- The enrolment of pediatric patients in clinical trials is ethically justifiable only when an expected benefit exists and the risks incurred are minimized. Otherwise, children should not be included in clinical trials.
- Since growth and weight gain are normal and expected developmental processes in the pediatric population, the assessment of efficacy for weight-loss drugs cannot rely on absolute weight reduction as in adults. Instead, efficacy must be evaluated relative to age- and sex-specific growth trajectories, such as standardized pediatric growth charts.

Strategic Approach and Solution

- Our regulatory strategy team designs a PIP to be discussed with the Pediatric Committee (PDCO) of the European Medicines Agency (EMA). Once agreed upon with the EMA, the same approach will be presented in a PSP to the FDA.
- The proposed PIP includes a waiver for the pediatric population from birth to 6 years of age. This should be acceptable based on precedents for similar products in the same indication.
- A juvenile repeat dose toxicity study in rats is planned to investigate potential detrimental effects on the developing nervous system and on sexual maturation.
- The MIDD experts adapt the existing adult population PK model to simulate exposure in adolescents (12 to 18 years) and children (6 to 11 years). This model allows to select doses that are expected to match adult exposure in defined age/body weight ranges and thus to be efficacious and safe for pediatric patients. Efficacy and safety simulations can be performed based on adult models for exposure-response (ER). Predictions of body weight trajectories take normal growth curves into account, and the resulting profiles must be interpreted within this developmental context. Weight stabilization during periods of expected growth may represent a clinically meaningful treatment effect.
- A small number of pediatric patients will be treated to confirm adequate exposure, efficacy and safety of the selected pediatric dose(s). The proposed PIP aims to agree on a deferral of this study post-approval.
- The MIDD experts will update the population PK and ER models using the newly generated data to refine predictions of drug exposure and response in pediatric patients. This refined model will support determining age/body weight-dependent doses to appropriately treat the pediatric population from 6 to 17 years of age through simulation.
- The safety assessment will be supported by the obtained data in pediatric patients and data from the toxicology study in juvenile animals. If a positive benefit/risk ratio is justified, the indication for children aged 6 to 12 years is pursued. Otherwise, the indication will be limited to adults and adolescents, which is the main target population.

Outcomes and Impact

- The early integration of MIDD expertise into the clinical program allows including the appropriate assessments in the planned Phase III study to assure an accurate characterization of PK and PD in adults through population PK and ER models.
- MIDD enables acceleration of pediatric development by leveraging PK data from adults. Scaling of adult PK profiles to children with lower body weight supports the selection of pediatric doses that are anticipated to achieve exposures consistent with those shown to be safe and efficacious in adults, thereby minimizing risk for pediatric trial participants.
- Since the primary aim of the pediatric cohort is to confirm model-based exposure predictions rather than independently characterize PK, efficacy, and safety, fewer pediatric participants are required to adequately inform dose selection.
- Updating the models with pediatric data allows for bridging of efficacy and safety from adults to adolescents and children aged 6 years and above, and for confirming or refining the dose selection in pediatrics. The overall safety evaluation is further supported with data from the juvenile animal toxicity study.
- The regulatory strategy team builds an evidence-based rationale to justify this approach and discusses it thoroughly with the regulatory authorities.
- Overall, this strategy allows for an agile and cost-effective development of a new product in pediatric patients. Assessment of efficacy and safety in these populations (adolescents and children) relies on very limited pediatric clinical data and animal data. Limiting the number of pediatric patients enrolled in clinical trials is possible by implementing an MIDD approach.

Do you need to design a Pediatric Development Plan?

Our team is ready to explore this collaboration in depth alongside you. If you are ready for a conversation, please **contact us.**

About PLG

> ProductLife Group is committed to offer integral solutions for the development of the most innovative therapies, considering the particularities of every single program. Our strength relies on bringing to our company some of the best boutique consulting firms around the world, in this case Zwiers Regulatory Consulting and IntiQuan, and building an ecosystem where they work together to offer seamless support in multiple aspects of drug development, well beyond the standard regulatory services. Our seasoned consultants team up to cover every aspect of your development program in due time with the right expertise, thus reducing risk and paving the best way for a successful approval.