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HOW TO PREPARE PAEDIATRIC INVESTIGATIONAL PLANS (PIPS): FOR ATMPS: KEY CLINICAL SCIENCE INSIGHTS

Advanced Therapeutic Medicinal Products (ATMPs)—which include gene therapies, cell therapies, and tissue-engineered products — represent a new frontier in medicine, particularly in addressing serious and life-threatening conditions. To ensure that these innovative therapies are safe and effective for children, the preparation of Paediatric Investigational Plans (PIPs) is crucial. Under Paediatric Regulation (EC) No 1901/2006, [1] all medicines seeking centralised marketing authorisation in the European Union (EU) must have an agreed-upon PIP by the time of submission unless a waiver or deferral is granted. An agreed PIP is typically required for any investigational medicinal product prior to the initiation of paediatric clinical trials. The Paediatric Committee (PDCO) of the European Medicines Agency (EMA) evaluates these PIPs on a case-by-case basis to ensure that sufficient data supports the use of ATMPs in a paediatric population. In this blog, I will briefly discuss key clinical considerations for PIP preparation when developing an ATMP for a paediatric population.

What is a PIP?

A PIP outlines how a new medicine, including ATMPs, will be studied in the paediatric population to demonstrate its safety and efficacy. A PIP must be submitted early in the drug development process, typically by the end of Phase I or pharmacokinetic studies, and no later than the start of Phase III clinical trials in adults. Given the novel and complex mechanisms of action in ATMPs, and that ATMPs often target severe, life-threatening diseases, the PIP plays a critical role in addressing long-term safety concerns, such as immunogenicity, biodistribution, and effects on growth and development.

ATMP-Specific Considerations for PIP

When developing a PIP for ATMPs, additional scientific considerations arise due to their complex and innovative nature. EMA's guideline for ATMPs [2] offers a thorough outline of the requirements for ATMP drug development. Below are key scientific considerations that are the most relevant for a PIP for ATMPs:

Long-term Safety and Monitoring

Given that children are still growing, long-term follow-up is critical to assess any delayed adverse effects and durability of the treatment in children.

- *Delayed toxicity:* Potential adverse effects may emerge years after treatment due to the ongoing growth of children and the potential amplification of genetic modifications introduced by ATMPs could increase over time. For example, ATMPs could have an increased risk of cancer due to the involvement of genetic modification, such as in gene therapy, where there is a potential risk for insertional mutagenesis (where inserted genes disrupt the host genome); or a higher chance to accumulate genetic mutations in the cell therapy where stem cells are used. Monitoring over an extended period is necessary to identify these risks.

- *Durability of Effect:* The duration of the therapeutic effect, and how the modified cells or transgenes behave over time must be evaluated. For gene therapies, the persistence of the therapeutic gene and its sustained expression over time needs to be closely monitored in children considering the growth of organs or cell turnover wherein genes have been inserted as well as children may have a longer life expectancy than adults, the effect could lessen.

Immune Response and Immunogenicity

ATMPs often involve introducing foreign genes, vectors, or cells into the body, triggering immunogenic responses. Children, especially younger ones, may have different immune responses compared to adults.

- *Immune tolerance:* younger patients may have developing or immature immune systems. The immune system's maturity at the time of treatment can affect how a child responds to the therapy, both in terms of efficacy and safety.
- *Pre-existing immunity:* In the case of viral vectors used in gene therapies, the level of pre-existing immunity to viral vectors, such as AAV, which could complicate treatment, may differ in children compared to adults. For infants and toddlers, it is important to retest anti-viral vector antibody titers, as detected antibodies may result from passive transfer of maternal neutralizing antibodies. These antibodies can decrease over the following weeks or months, potentially allowing treatment at a later stage.
- *Immunomodulation strategies:* The need for immune suppression or modulation, particularly in the case of allogenic cell therapies, must be carefully balanced in paediatric populations to avoid compromising the child's developing immune system.

Biodistribution and Safety

- *Biodistribution:* ATMPs are often designed as localised or targeted treatments. The biodistribution of ATMPs, including where the product localises in the body and how long it remains active, varies in children due to age-related physiological differences. These ATMPs therefore have the potential to affect developing organs/tissues in children differently than in adults. For example, gene therapy for a liver-targeted disease should take into account the relatively large liver size and higher metabolic activity in children than in adults, which can impact viral vector distribution within and act upon liver cells.
- *Neurological targets:* Many ATMPs target neurodegenerative or neuromuscular disorders in children. For therapies with neurological targets, the blood-brain barrier (BBB) maturation is difficult to compare between different species, thus the use of animal safety data is difficult to assess safety. There are also limited data on BBB permeability particularly in younger children, which adds complexity to safety and efficacy assessment.

Use of Extrapolation

In certain cases, extrapolating data from adult trials to support paediatric drug development can be justified, depending on the underlying mechanism of action of the ATMPs. The Reflection Paper on *Paediatric Extrapolation [3]* by EMA aims to reduce the burden on paediatric drug development and provides the guidance on:

- *Justification for extrapolation:* a robust rationale for extrapolating adult data is required while considering the physiological differences between children and adults.
- *Bridging studies:* If full extrapolation is not possible, conduct bridging studies to fill in the gaps in paediatric data. These studies require thoughtful trial designs to determine how much adult data can be applied to the situation or translated to the target paediatric population, and what additional data is required specifically for the paediatric population.

Innovative Trial Design and Endpoints

- *Innovative Trial Designs:* Adaptive trial designs and real-world evidence may be used to accelerate paediatric ATMP development while ensuring patient safety. Registries and natural history studies may help reduce the need for placebo-controlled trials, which might be ethically challenging in severe and rare paediatric diseases. Since ATMPs frequently target rare diseases, innovative trial designs can aid in planning statistically meaningful outcomes in small populations, or even support an underpowered trial that demonstrates clinically relevant outcomes on a per-patient basis.
- *Paediatric-Specific* Endpoints: Identifying appropriate clinical endpoints for paediatric trials, especially for rare and severe diseases, is often challenging. For younger children, developmental milestones, physiological measures, or behavioral scales can be considered as endpoints in place of gold standard outcomes in adult trials. For rare diseases, involving caregivers and healthcare providers to identify usable and relevant endpoints can be considered.

- *Patient-Centered Outcomes:* For ATMPs targeting paediatric populations, especially those with rare, progressive diseases, patient-centered outcomes such as quality of life and functional independence may be critical endpoints in clinical trials. Quality of life improvements should be obtained from both the children's and the caregiver's perspective, particularly when the treatment affects long-term development.

Conclusion

PIPs are essential to ensure that paediatric clinical trials are designed to meet regulatory requirements while addressing the scientific and clinical challenges of ATMP development. ATMPs, with their innovative mechanisms and potential to transform treatment for life-threatening conditions, demand careful planning through the PIP process to optimise their long-term success across all age groups.

Paediatric development of ATMPs is both fascinating and complex, as highlighted in this blog. There are many factors to consider, and if you have any questions, feel free to reach out to me or my colleagues at 3D-PharmXchange. Our team brings a wealth of experience across the entire spectrum of drug development, including nonclinical, Chemistry, Manufacturing, and Controls (CMC), clinical, and regulatory affairs. We offer comprehensive support in the preparation of PIPs, ensuring alignment with regulatory requirements while addressing the unique challenges posed by advanced therapies. Several of our senior consultants specialized in ATMP development and have a proven track record of guiding sponsor through the intricacies of each development phase. We will tailor our approach to meet your project's specific needs. Whether you are navigating complex regulatory landscapes or addressing clinical or technical hurdles, 3D-PharmXChange team is equipped to streamline the process and deliver strategic insights to support your success.

References

1. EMA. Regulation (EC) No 1901/2006 of the European Parliament and of the Council on 12 December 2006 on Medicinal Products for Paediatric Use and Amending Regulation (EEC) No 1768/92, Directive 2001/20/EC, Directive 2001/83/EC and Regulation (EC) No. 726/2004 https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A32006R1901&qid=1621344437946 (27 Dec. 2006).

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3. EMA. EMA/189724/2018, Reflection Paper on the Use of Extrapolation in the Development of Medicines for Paediatrics—Final https://www.ema.europa.eu/en/documents/scientific-guideline/adopted-reflection-paper-use-extrapolation-development-medicines-paediatrics-revision-1_en.pdf (7 Oct. 2020).