RF Quarterly

Volume 3 • Number 4

Pediatric drug development: Essential insights for success

Kimberly Belsky, MS, FRAPS

Karl-Heinz Huemer, MD, PhD

Linda McBride, RPh, RAC

This article describes some of the key considerations in establishing a global pediatric drug development strategy, including changes in regulatory requirements and clinical study design, and includes case studies and examples.

Keywords – pediatric drug development, strategy, precedent, study design

Introduction

Pediatric drug development in the US and EU is subject to the continual evolution in local, regional, and global regulatory requirements and guidelines. While these changes may take time to implement, it is paramount that regulatory professionals routinely monitor regulatory changes and shifts in precedent to ensure the development of robust strategies that include risk and mitigation plans for pediatric drug development. Failure to do so can lead to delays in clinical study conduct, compliance issues, and missed opportunities for new and enhanced pediatric treatment options.

Monitoring changes in the regulatory environment

Regulations and guidance

There were several important proposed changes in the EU and US regulatory environments during 2023, each of which could affect pediatric drug development programs and warrants monitoring for finalization and implementation of specific regulations.

In April 2023, the European Commission published a proposal to reshape the regulation of the EU pharmaceutical sector[1] by addressing inequities around new medicines, including their availability to patients, drug pricing, transparency related to public funding of drug development, environmental sustainability, drug shortages, and global competitiveness.[2] The proposal amends and replaces the existing EU directive and regulation and the regulation of pediatric and orphan drugs and includes recommendations for:

- Revision of data protection periods, exclusivity, and incentives;
- The introduction of a new pediatric investigation plan that will evolve and become more defined as more evidence becomes available; and
- Simplifying the EMA's delegate structures by discontinuing the orphan, pediatric, and advanced therapy medicinal products committees and retaining just two scientific committees – the Committee for Medicinal Products for Human Use, for approving human medicines, and the Pharmacovigilance Risk Assessment Committee, for assessing human safety data.

In May 2023, the FDA issued two important draft guidance documents addressing the regulatory[3] and scientific[4] considerations in pediatric drug development. The documents are intended to clarify the agency's approach to requirements and incentives related to drug development for this population, though obtaining pediatric exclusivity could become more challenging.

The draft guidance on regulatory considerations[3] describes the process for qualifying for pediatric exclusivity under the Best Pharmaceuticals for Children Act (BPCA),[5] including the intent to limit the scope of studies eligible for pediatric market exclusivity under the BPCA. Historically, the FDA has periodically granted pediatric market exclusivity to sponsors conducting studies already required under the Pediatric Research Equity Act (PREA),[6] even if no new indications were expected in a pediatric population. The guidance notes that written requests from the agency would be reserved only for sponsors who need to conduct additional studies beyond PREA requirements to demonstrate a drug's health benefits in the pediatric population.[3] Thus, under the final document, the FDA will likely not issue written requests for drugs for studies or planned studies required under the PREA.

The draft guidance on scientific considerations[4] clarifies the clinical, scientific, and ethical issues related to the development of pediatric drugs and biologics under the BPCA and PREA, specifically regarding formulation development, clinical and nonclinical information, safety information, and the conditions under which sponsors may extrapolate pediatric data from studies of drugs intended for adult use.

End points and data acceptability

The EMA and FDA share many similarities in their evaluation processes, but there can be instances in which they may not accept the same end points and outcomes. This divergence can occur because of differences between EU and US regulatory priorities, patient populations, and healthcare systems. For example, the EMA might be more open to accepting certain clinical end points or surrogate markers as valid indicators of a drug's efficacy, especially in cases in which there is a significant unmet medical need or the benefits outweigh the risks for the European patient population.

One such example was the June 2021 expanded indication authorization in the EU for Aubagio (teriflunomide)[7] as a first-line treatment for relapsing-remitting multiple sclerosis (RRMS) in patients aged 10 to 17 years. The EU approval came after the FDA had issued the company a complete response letter[8] for the same patient population. The FDA deemed the submitted data were not sufficient for obtaining approval of an indication in the pediatric population, and the Aubagio label[9] was updated in 2021 to include safety data from the pediatric clinical study program. Specifically, Subsection 5.11 of the label's Warnings and Precautions section was revised to include a warning for pancreatitis in pediatric patients, and Subsection 8.4 of the Use in Specific Populations section was revised to reflect that the drug's safety and effectiveness had not been demonstrated in the clinical study evaluating pediatric patients with RRMS.[10]

> *Sponsors might consider using the EMA-FDA parallel scientific advice program to ensure potential strategies align with the preferences of the two agencies.*

Such differences between the EU and US underscore the importance of carefully navigating the regulatory requirements and understanding the regulatory flexibility of the respective authorities to ensure successful drug approval in both places. Sponsors should engage with all relevant agencies early in the drug development phase to proactively identify and address potential problems. They might consider using the EMA-FDA parallel scientific advice program to ensure potential strategies align with the preferences of the two agencies. In general, staying informed and adapting to regulatory

changes is integral to any pediatric drug development program.

Rare diseases with simultaneous approval in adults

A company can request the FDA assign a pediatric drug any of the following designations, which could facilitate its development and have a positive impact on final product approval:

- **Orphan drug,** introduced in the Orphan Drug Act of 1983;[11]
- **Fast track,** introduced in the Food and Drug Administration Modernization Act;[12]
- **Regenerative medicine advanced therapy (RMAT),** introduced in the 21st Century Cures Act;[13] and
- **Rare pediatric disease (RPD),** introduced in the Food and Drug Administration Safety and Innovation Act.[14]

As of November 2023, the FDA has approved several products for rare diseases with indications for both pediatric and adult patients. The following approvals are examples of how FDA designations had a positive effect, facilitating the development and path to approval:

- **Vyjuvek (beremagene geperpavec-svdt),** approved on 19 May 2023,[15] was granted designations of orphan drug, fast track, RMAT, and RPD. The biologics license application (BLA) received priority review, and the manufacturer, Krystal Biotech, received a priority review voucher (PRV) upon approval. The approval was the first for a topical gene therapy for treating epidermolysis bullosa in patients six months or older.[16]
- **Skyclarys (omaveloxolone),** approved on 28 February 2023,[17] was granted designations of orphan drug, fast track, and RPD. The new drug application (NDA) received priority review, and the manufacturer, Reata Pharmaceuticals, received a PRV upon approval. The approval was the first for treating Friedreich's ataxia in patients aged 16 years or older.[18]
- **Veopoz (pozelimab-bbfg)** was approved on 18 August 2023 for treating CHAPLE disease in patients one year old or older.[19] It was granted designations of orphan drug, fast track, and RPD. The NDA received priority review, and the manufacturer, Regeneron, received a PRV upon approval.
- **Daybue (trofinetide)** was approved on 10 March 2023[20] for treating Rett syndrome in adults and pediatric patients aged two years or older. It was granted designations of orphan drug, fast track, and RPD. The NDA received priority review, and the manufacturer, Acadia Pharmaceuticals, received a PRV upon approval.
- **Joenja (leniolisib)** was approved on 24 March 2023[21] for treating activated phosphoinositide 3-kinase delta syndrome in adults and pediatric patients 12 years or older. It was granted designations of orphan drug and RPD. The NDA received priority review, and the manufacturer, Pharming Technologies, received a PRV upon approval.

Understanding the benefits, criteria, and timing for the various avenues provided by the FDA is critical to the overall drug development program and corporate objectives.

Receiving an RPD designation and the subsequent receipt of a PRV upon approval is a lucrative benefit. The company can use the PRV in future NDA or BLA submissions to facilitate a priority review rather than the standard review, reducing the review from 10 months to six months. A PRV can also be sold to another company – one company recently sold its PRV for $102 million.[22] Understanding the benefits, criteria, and timing for the various avenues provided by the FDA is critical to the overall drug development program and corporate objectives.

Clinical study design

There are numerous challenges in designing a clinical study (or studies) for approving a drug in the pediatric population, especially for products that have already been approved. A hypothetical example would be an investigational product with a potential topical analgesic effect (based on its mechanism of action). In this example, the following considerations would need to be addressed:

- **The effects of administration route and duration of treatment.** A locally or topically treated indication will likely require short-term treatment (e.g., for simple surgical procedures or local infections). Long-term conditions would more likely require a systemic treatment. These short- and long-term considerations should have a role in defining and justifying an appropriate patient population for inclusion in the study, bearing in mind that the planned label should always address whether the new therapy will meet an unmet therapeutic need in this target population. When developing drugs for children, it is important to strike a balance between limiting development to an older population and expanding the scope of the study to include all ages, despite the challenges of doing so. Early discussion with the regulatory agency about approaches to age inclusivity is recommended.
- **Appropriate outcome measures in different age ranges.** In the current example, the study design for a locally acting analgesic in children poses specific problems, such as which end points would be appropriate if younger children were included in the patient population. Established adult outcome measures, such as the visual analog or Likert scales, are not applicable in the pediatric setting. Instead, an innovative approach would be required, such as involving healthcare providers in reporting pediatric patient outcomes by, for example, noting their patients' behavioral or even autonomic reactions to pain.
- **Disease progression patterns.** For recurrent and multiple lesions (e.g., in epidermolysis bullosa), it would be important to ensure that patients' current standard-of-care and other adjunctive treatments, such as antiseptics or those for wound healing, are not interrupted. This can be addressed by isolating treatment with the study drug/topical analgesic to an established number of predefined target lesions or predefined area(s) of the body that are tracked for comparison with untreated lesions or body areas. One should also consider whether comparative data for other established analgesics might be required in the study. Pediatric-specific problems will also have to be addressed, for example, compliance with often burdensome wound management or nonspecific reporting of disease symptoms.

> *When developing drugs for children, it is important balance limiting development to an older population and expanding the scope of the study to include all ages.*

In conclusion, pediatric studies will require some specific considerations in addition to the aspects that usually have to be taken into account for adult-only trials.

Age-appropriate formulations

Another important aspect of pediatric drug development is the establishment of age-appropriate formulations for the age ranges in which the product will be used. Both US and EU regulations specify that this can be imposed.[3,23]

It is important to start such considerations early. This would include a critical review of all excipients planned for use in the pediatric formulations to assess their possible risks if included. Only essential excipients should be included and, where warranted, replaced with those

that have better-established safety profiles in children. These products could include dyes, sweeteners, stabilizers, parabens, alcohol, and flavorings. Requirements for excipients in pediatric drug development are much stricter than in other regulated industries, for example, those in prepared foods. It should be noted that considerations around excipients in the pediatric setting may also be relevant to adult formulations of the same drug and that a formulation appropriate for children might also be preferable for adults.

Tablet size should be age appropriate so that younger children can easily and safely swallow the tablet and to ensure accurate dosing. Other formulation options – such as microtablets, granules, or liquids – that will ensure ease and safety of swallowing and accurate dosing may also need to be considered. Acceptability of the formulation will require supporting data in the target population, mainly as a secondary objective in the clinical study. There may be a need for more than one additional formulation. This could include having smaller tablet sizes or strengths for more accurate dosing and/or to allow easier swallowing in smaller children or microgranules for sprinkling on food or adding to liquid formulations for infants. The microgranular formulation would also need proof of appropriate bioavailability.

Conclusion

Pediatric drug development is complex and requires multifaceted strategic considerations to achieve success. Early engagement with health authorities is a strategic imperative and requires internal collaboration to ensure alignment on selecting the end point(s), the age ranges for the study groups, and the formulation needs of pediatric patients while also achieving the company goals. This strategy encompasses an understanding of the current and evolving global regulatory requirements and incentives and an assessment of current precedent to ensure success.

Abbreviations

BLA, biologics license application; **BPCA,** Best Pharmaceuticals for Children Act; **EMA,** European Medicines Agency; **FDA,** Food and Drug Administration [US]; **NDA,** new drug application; **PREA,** Pediatric Research Equity Act; **PRV,** priority review voucher; **RMAT,** regenerative medicine advanced therapy; **RPD,** rare pediatric disease.

About the authors

Kimberly (Kim) Belsky, MS, FRAPS, is an experienced regulatory professional skilled in innovative and strategic thinking as it relates to a range of medical products and functional areas. Her global roles include regulatory policy and intelligence and advertising and promotion. Her passion is the assessment of changes in the regulatory environment to identify opportunities and challenges. Belsky holds a master of science degree in chemistry from State University of New York at Stony Brook and has several scientific publications. She served as chair for the 2022 and 2023 RAPS Convergence meetings and on the RAPS board of directors during 2021-2023. She can be reached at belskyk@yahoo.com

Karl-Heinz Huemer, MD, PhD, is a regulatory and scientific consultant. He studied medicine at the Medical University of Vienna, where he completed internships in clinical pharmacology and ophthalmology while completing his medical degree. After obtaining a PhD in biology from the University of Vienna, he worked for more than 20 years as a physiologist at the Medical University of Vienna as a researcher and teacher. He has served as a member of the ethics committee of the University Clinics. In 2007, Huemer became a clinical assessor at the Austrian Medicines & Medical Devices Agency and was subsequently appointed as a delegate to the EMA's Paediatric Committee and Scientific Advice Working Party where, over 15 years, he gained a broad expertise in most therapeutic areas by assessing close to 400 pediatric investigation plans about scientific advice procedures. Huemer is a regular contributor to RAPS events in the US and EU. He can be reached at karl-heinz@khhuemer.com

Linda McBride, RPh, RAC, is a partner at IAA Consulting, with extensive experience in the science of drug development in the biopharmaceutical industry. Her expertise is in the development and implementation of registration strategies for drug and biologics in various therapeutic areas, from candidate selection through marketing application and postapproval during her career of more than 30 years. McBride is a RAPS member and serves on the society's editorial advisory and Convergence planning committees. She frequently presents on pediatric drug development at RAPS events and has edited numerous RAPS books, including co-editing the 2023 edition of Fundamentals of Pharmaceutical and Biologics Regulations: A Global Perspective. She can be reached at linda@iaaconsultingllc.com

Acknowledgment

This article was adapted from a presentation by the authors at the RAPS Convergence 2023 in Montreal, QC from 3-5 October.

Citation Belsky K, et al. Pediatric drug development: Essential insights for success. RF Quarterly. 2023;3(4):4-10. Published online 8 December 2023. https://www.raps.org/News-and-Articles/News-Articles/2023/12/Pediatric-drug-development

References

All references last checked and verified on 15 November 2023.

European Health Union: Commission proposes pharmaceuticals reform for more accessible, affordable and innovative medicines [press release]. European Commission. Dated 26 April 2023. https://ec.europa.eu/commission/presscorner/detail/en/ip_23_1843

1. European Commission. Reform of the EU pharmaceutical legislation. Dated 26 April 2023. https://health.ec.europa.eu/medicinal-products/pharmaceutical-strategy-europe/reform-eu-pharmaceutical-legislation_en
2. Food and Drug Administration. Pediatric drug development: Regulatory considerations – Complying with the Pediatric Research Equity Act and qualifying for pediatric exclusivity under the Best Pharmaceuticals for Children Act [draft guidance]. Dated May 2023. https://www.fda.gov/media/168201/download
3. Food and Drug Administration. Pediatric drug development under the Pediatric Research Equity Act and the Best Pharmaceuticals for Children Act: Scientific considerations [draft guidance]. Dated May 2023. https://www.fda.gov/media/168202/download
4. Food and Drug Administration. Best Pharmaceuticals for Children Act (BPCA). Current as of 25 September 2018. https://www.fda.gov/drugs/development-resources/best-pharmaceuticals-children-act-bpca#:~:text=BPCA%20provides%20an%20incentive%20of,Written%20Request%20issued%20by%20FDA
5. Food and Drug Administration. Pediatric Research Equity Act (PREA). Current as of 7 November 2019. https://www.fda.gov/drugs/development-resources/pediatric-research-equity-act-prea
6. European Medicines Agency. Aubagio. European public assessment report. Last updated 22 August 2023. https://www.ema.europa.eu/en/medicines/human/EPAR/aubagio
7. Sanofi provides update on Aubagio (teriflunomide) submission for children and adolescents with relapsing-remitting multiple sclerosis in the US [press release]. Sanofi. Dated 11 June 2021. https://www.sanofi.com/en/media-room/press-releases/2021/2021-06-11-05-00-00-2245628
8. Aubagio. Prescribing information. Genzyme Corp. Revised April 2021. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/202992s013s015lbl.pdf
9. Food and Drug Administration. Aubagio. Supplement approval and fulfillment of postmarketing requirement. Dated 30 April 2021. https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2021/202992Orig1s013,%20s015ltr.pdf
10. Food and Drug Administration. Designating an orphan product: Drugs and biological products. Current as of 8 July 2022. https://www.fda.gov/industry/medical-products-rare-diseases-and-conditions/designating-orphan-product-drugs-and-biological-products
11. Food and Drug Administration. Fast track. Current as of 4 January 2018. https://www.fda.gov/patients/fast-track-breakthrough-therapy-accelerated-approval-priority-review/fast-track
12. Food and Drug Administration. Regenerative medicine advanced therapy designation. Current as of 21 July 2023. https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/regenerative-medicine-advanced-therapy-designation
13. Food and Drug Administration. Rare pediatric disease (RPD) designation and voucher programs. Current as of 2 June 2023. https://www.fda.gov/industry/medical-products-rare-diseases-and-conditions/rare-pediatric-disease-rpd-designation-and-voucher-programs
14. Food and Drug Administration. Vyjuvek. Product information and supporting documents. Current as of 7 August 2023. https://www.fda.gov/vaccines-blood-biologics/vyjuvek
15. Food and Drug Administration. FDA approves first topical gene therapy for treatment of wounds in patients with dystrophic epidermolysis bullosa [press release]. Dated 19 May 2023. https://www.fda.gov/news-events/press-announcements/fda-approves-first-topical-gene-therapy-treatment-wounds-patients-dystrophic-epidermolysis-bullosa#:~:text=Today%2C%20the%20U.S.%20Food%20and,1%20chain%20(COL7A1)%20gene
16. Food and Drug Administration. Skyclarys. NDA approval. Dated 28 February 2023. https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2023/216718Orig1s000ltr.pdf
17. Food and Drug Administration. FDA approves first treatment for Friedreich's ataxia. Current as of 28 February 2023. https://www.fda.gov/drugs/news-events-human-drugs/fda-approves-first-treatment-friedreichs-ataxia
18. Food and Drug Administration. Veopoz. BLA approval.

Dated 18 August 2023. https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2023/761339Orig1s000ltr.pdf
19. Food and Drug Administration. Daybue. NDA approval. Dated 10 March 2023. https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2023/217026Orig1s000ltr.pdf
20. Food and Drug Administration. Joenja. NDA approval. Dated 24 March 2023. https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2023/217759Orig1s000ltr.pdf
21. Sarepta Therapeutics announces sale of priority review voucher for $102 million [press release]. Sarepta Therapeutics. Dated 5 July 2023. https://investorrelations.sarepta.com/news-releases/news-release-details/sarepta-therapeutics-announces-sale-priority-review-voucher-102
22. Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 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/PDF/?uri=CELEX:32006R1901