FDA Continues to Strengthen Paediatric Study Expectations

After a three-year reprieve, a new US paediatric study requirement kicks in on August 18, 2020, for sponsors of certain molecularly targeted oncology drugs.

The US Food and Drug Administration (FDA) Reauthorization Act of 2017 (FDARA) introduced the requirement, which applies to new drug applications (NDAs) and biologics license applications (BLAs) for any new, molecularly targeted cancer drug or biologic that is 1) intended to treat an adult cancer and 2) directed at a molecular target that is "substantially relevant to the growth or progression of a paediatric cancer."[1] FDARA gave sponsors three years to adjust to the new provision – but that delay is coming to an end, and sponsors soon must incorporate molecularly targeted paediatric cancer investigations into development programmes and submit results in applications for approval.

The FDARA requirement is meant to ensure there are early paediatric investigations of molecularly targeted cancer drugs that have the potential for anti-tumour efficacy in babies, children, and adolescents, to speed an understanding of both their potential effectiveness and toxicities. The requirement applies even when an adult cancer indication does not appear in paediatric patients – and it ends a provision exempting orphan cancer drugs from paediatric study requirements.

Relevant Regulations

The FDA's authority to require paediatric safety and efficacy studies for certain drugs and biological product applications stems from the Pediatric Research Equity Act (PREA) of 2003.[2] PREA applies to applications "for a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration". PREA studies must:

- Use age-appropriate formulations,
- Assess safety and effectiveness "in all relevant paediatric subpopulations", and
- Be adequate to support dosing and administration in subpopulations where safety and effectiveness are established.

PREA allows sponsors to extrapolate paediatric efficacy from adequate and well-controlled studies conducted in adults if the disease course and drug effects are "sufficiently similar". The FDA can waive a product from PREA requirements if studies are "impossible or highly impracticable"; evidence "strongly" suggests the product would be ineffective or unsafe in paediatric patients; or if the product does not offer "meaningful therapeutic benefit" over existing treatments or is unlikely to be used in a "substantial number" of paediatric patients.

Until 2017, PREA also stated an exception to paediatric study requirements: in an attempt to incentivise drug development for orphan diseases, PREA exempted drugs with orphan indications. FDARA changed that when Title V – also called the Research to Accelerate Cures and Equity (RACE) for Children Act – eliminated the orphan exemption for cancer drugs directed at certain molecular targets.

Historically, requirements for paediatric studies of new cancer drugs were based on a product's indication: if a product was intended for use in paediatric patients, studies were to be conducted in the relevant paediatric subpopulations. Under FDARA, the requirement for a "molecularly targeted paediatric cancer investigation" is based on the proposed product's *molecular mechanism of action*, not its indication. The law directs the FDA (in collaboration with several groups, including the National Cancer Institute) to "establish, publish, and regularly update" a "Relevant Molecular Target List" and a "Non-Relevant Molecular Target Leading to Waiver List".[3]

New FDA Draft Guidances Are Intended to Help Sponsors Adjust

The FDA recently published two draft guidances intended to help oncology drug sponsors understand and implement the FDARA paediatric study requirement.

FDARA Implementation Guidance for Pediatric Studies of Molecularly Targeted Oncology Drugs: Amendments to Sec. 505B of the FD&C Act, published in December 2019, gives an overview of FDARA requirements and how to fulfill them. It also discusses the relevant and non-relevant molecular target lists and how the FDA updates them; the content of an initial paediatric study plan (iPSP); recommendations for studies; special considerations for rare cancers; and situations in which a waiver or deferral may be granted.

Pediatric Study Plans for Oncology Drugs: Transitional Information Until Full Implementation of FDARA Section 504, published in January 2020, is written in question-and-answer (Q&A) form. In it, the FDA responds to some of the queries received since FDARA was enacted in 2017. Topics addressed include:

- How requirements vary before and after August 18, 2020.
- When an iPSP is required and when an abbreviated iPSP is acceptable.
- iPSP and study requirements for drugs in cross-labelled oncology drug combination regimens.

The Orphan Drug "Loophole"

The new draft guidance documents follow other FDA actions aimed at strengthening paediatric study requirements. For example, the FDA intended its December 2017 final guidance, *Clarification of Orphan Designation of Drugs and Biologics for Pediatric Subpopulations of Common Diseases*, to "close a loophole" in PREA that enabled sponsors to skirt requirements for paediatric studies, according to a September 2017 "FDA Voices" column by then-FDA Commissioner Scott Gottlieb, MD.

The loophole became apparent when sponsors sought and obtained orphan designation for paediatric subtypes of "otherwise common and non-orphaned" adult diseases, Gottlieb explained.

Once a sponsor attained paediatric orphan designation for a drug, the product became exempt from PREA requirements — it never had to be studied in paediatric patients.

"In effect, by letting sponsors designate paediatric subpopulations of drugs intended to treat adult diseases, the drug makers receive an unintended 'free pass' from having to study drugs in these or other paediatric uses," Gottlieb wrote. "Thus, rather than ensuring more paediatric research, as Congress envisioned, we can end up with fewer paediatric studies."

In the FDA's introduction to *Clarification of Orphan Designation of Drugs and Biologics for Pediatric Subpopulations of Common Diseases*, the agency states that it "does not expect to grant any additional orphan-drug designation to drugs for paediatric subpopulations of common diseases."

REFERENCES

1. Section 504 of FDARA amended section 505B of the Federal Food, Drug, and Cosmetic (FD&C) Act.
2. PREA is codified at section codified at 505B of the FD&C Act.
3. Both lists are available at: https://www.fda.gov/AboutFDA/Centers Offices/OfficeofMedicalProductsandTobacco/OCE/ucm544641.htm

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