Development of Anti-Infective Drug Products for the Pediatric Population

Guidance for Industry

U.S. Department of Health and Human Services
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Center for Drug Evaluation and Research (CDER)
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Development of Anti-Infective Drug Products for the Pediatric Population Guidance for Industry[1]

This guidance represents the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA office responsible for this guidance as listed on the title page.

I. INTRODUCTION

The purpose of this guidance is to provide general recommendations on the development of anti-infective drug products,[2] including antibacterial, antifungal, and antiparasitic products, for the pediatric population.

FDA encourages sponsors to discuss their initial pediatric study plans (iPSPs) for anti-infective drug products with the Agency early. In most instances, iPSPs must be submitted no later than 60 calendar days after the end-of-phase 2 meeting.[3]

This guidance does not address the full scope of considerations for pediatric anti-infective drug product development. More detailed information on clinical pharmacology considerations for neonatal and pediatric studies (e.g., sample size, pharmacokinetic sampling, data analysis) is available in several guidances for industry.[4] This guidance also does not apply to preventative

[1] This guidance has been prepared by the Division of Anti-Infectives in the Center for Drug Evaluation and Research, in cooperation with the Center for Biologics Evaluation and Research (CBER), at the Food and Drug Administration.

[2] For the purposes of this guidance, all references to *drug products* include both human drugs and biological products unless otherwise specified. Sponsors are encouraged to discuss individual drug product differences with the Division of Anti-Infectives or the applicable review division in CBER during drug product development.

[3] See section 505B(e)(2)(A) of the Federal Food, Drug, and Cosmetic Act (FD&C Act); 21 U.S.C. 355c(e)(2)(A). See also the guidance for industry *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Initial Pediatric Study Plans* (July 2020). We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

[4] See the draft guidances for industry *General Clinical Pharmacology Considerations for Neonatal Studies for Drugs and Biological Products* (July 2019) and *General Clinical Pharmacology Considerations for Pediatric Studies for Drugs and Biological Products* (December 2014). When final, these guidances will represent the FDA's current thinking on these topics. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

vaccines. The general principles set forth in this guidance apply to drug and biological products. However, because of the complexity and limited experience with some biological products regulated by the Center for Biologics Evaluation and Research (CBER) (e.g., cellular and gene therapies, phage therapies), there may be additional development considerations. In such cases, CBER encourages sponsors to reach out to the applicable review division, as appropriate.

The contents of this document do not have the force and effect of law and are not meant to bind the public in any way, unless specifically incorporated into a contract. This document is intended only to provide clarity to the public regarding existing requirements under the law. FDA guidance documents, including this guidance, should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidance means that something is suggested or recommended, but not required.

II. BACKGROUND

It is important to conduct clinical studies in the pediatric population to inform dosing and assess the safety and efficacy of anti-infective products. Challenges with pediatric drug development often include the following:

- In addition to the effects of body size, developmental changes in neonates and young children (e.g., maturation of organ function, changes in body fluid composition) can affect the absorption, distribution, metabolism, and excretion of drug products.

- Unique manifestations of some infectious diseases in neonates and infants, as compared to adults and older children, may affect anti-infective drug product development for this younger pediatric population.

- Because of logistical and ethical concerns, there may be limited ability to obtain samples for laboratory tests (e.g., blood, cerebrospinal fluid) from pediatric trial participants.

III. DRUG PRODUCT DEVELOPMENT CONSIDERATIONS

Sponsors should consider the following when developing anti-infective drug products for the pediatric population:

- Efficacy extrapolation:

    — Efficacy results from adequate and well-controlled clinical trials in adult participants can be extrapolated to a pediatric patient population if:

        - The course of the infectious disease is similar in adult and pediatric populations[5] (e.g., complicated intra-abdominal infections, complicated urinary tract infections,

[5] Section 505B(a)(2)(B)(i) of the FD&C Act.

community-acquired bacterial pneumonia, acute bacterial skin and structure infections). This implies a similar disease process, including the organisms recovered from the site of infection.

AND

- The effects of the drug product are sufficiently similar in adult and pediatric populations.[6] In general, for anti-infective drug products, activity against an organism is similar regardless of the host once drug product exposure at the site of infection is adequate.

Even when efficacy can be extrapolated, pediatric data will be warranted to assess the safety and pharmacokinetics of the drug product. The sponsor should demonstrate that the proposed dosing regimen results in similar exposures in pediatric participants as in adult participants. Because most anti-infective therapies are prescribed for a short course of treatment, sponsors may be able to obtain some efficacy information from these studies.

— For infections in which the pathophysiology and clinical manifestations of the disease are different between adult and pediatric populations or between the different subgroups in the pediatric population, reliance solely on efficacy demonstrated in adult participants may not be appropriate. For example, invasive candidiasis in neonates[7] has a more severe clinical course than in adults and older children, including a greater likelihood of dissemination to the central nervous system. Therefore, it would not be possible to extrapolate efficacy of a drug product studied only in adult and older pediatric populations for the treatment of invasive candidiasis to neonates.

- When efficacy cannot be extrapolated from adult or older pediatric populations to younger pediatric populations, adequate and well-controlled clinical trials may be needed to support the indication.

- Cohorts based on age, body weight or body surface area:

— Phase 3 clinical trials in adult participants should include adolescent participants (12 years and older) when there are sufficient safety data from adults to assess the risks and the prospect of direct benefit for the adolescent participants. Where appropriate from a scientific and ethical perspective, FDA strongly encourages sponsors to enroll adolescent participants in adult trials.

— Cohorts for pediatric studies should be determined based on the incidence of the disease and any specific considerations for the drug product under evaluation, such as

[6] Section 505B(a)(2)(B)(i) of the FD&C Act.

[7] See the International Council for Harmonisation (ICH) guidance for industry *E11(R1) Addendum: Clinical Investigation of Medicinal Products in the Pediatric Population* (April 2018).

factors that may influence pharmacokinetics or safety. Sponsors can define cohorts based on criteria other than chronological age (e.g., weight, body surface area).

— FDA encourages enrollment of some age cohorts in parallel rather than in sequence for drug products that do not have specific safety concerns or pharmacokinetic (PK) properties that warrant a sequential approach. Sponsors should discuss such enrollment with the Agency.

— Neonates (including extremely low birth weight infants) present challenges for dosing considerations[8] to achieve drug exposures required for efficacy and to assess exposures associated with toxicities. Sponsors should enroll neonatal participants after establishing the dose(s) for the older pediatric cohorts.

— The sponsor should consider the need to assess the effect of obesity on dose selection.

- Safety data:

— In general, the sponsor should collect safety data using the intended dose and duration of use of the drug product.

— In cases where an anti-infective drug is being developed for a pediatric-specific indication (e.g., acute bacterial otitis media), FDA recommends that sponsors provide supportive safety and efficacy data if available from adult participants with a related indication (e.g., acute bacterial sinusitis). Sponsors should discuss their development plans with the Agency.

— Safety data from nonclinical studies, known safety signals from the drug class, and the safety profile in adults can provide supportive information and identify adverse events of interest for evaluation in pediatric studies. However, certain toxicities may affect developmentally immature organ systems and tissues that are unique to the pediatric population, with increasing risk likely with decreasing age. These situations may merit additional safety assessments.

— The size of the recommended pediatric safety database of a drug product depends on several considerations in addition to those noted above, including the incidence of the disease, adverse event profile of the drug product or drug class, and expected use of the drug product in the pediatric population. Sponsors should discuss the size of the safety database with the Agency as the clinical development of the drug product proceeds.

— In general, pediatric studies of anti-infective drug products use an active comparator that is considered standard of care (SoC) at the trial site and may include different

[8] See the ICH guidances for industry *E11 Clinical Investigation of Medicinal Products in the Pediatric Population* (December 2000) and *E11(R1) Addendum: Clinical Investigation of Medicinal Products in the Pediatric Population* (April 2018).

comparators at different trial sites. In these trials, treatment allocation with unequal randomization with more subjects in the experimental arm versus SoC is acceptable.

— Safety data from a comparative pediatric study (e.g., new drug product versus SoC) may be needed for a drug product with limited data (e.g., a new drug class) or concerning findings (e.g., toxicity findings in nonclinical studies).

— Although comparative safety data are more interpretable, if appropriate from a regulatory perspective, a noncomparative study may be considered acceptable for a drug product in a known class with a well-characterized safety profile in adults and children.

— If the dose and duration of treatment are similar across different indications, the sponsor can use safety data from one indication to support the safety data for other indications.

- Additional considerations for studies in pediatric populations include the following:

— For pediatric studies that are intended mainly to evaluate safety and/or pharmacokinetics, there can be some flexibility in the inclusion and exclusion criteria, such as duration of prior antibacterial therapy, and choice of comparators based on SoC at the enrolling site. Sponsors should discuss inclusion and exclusion criteria for enrollment in pediatric studies with the Agency.

— In single-dose studies intended to assess the pharmacokinetics of a drug product, if the disease state is not expected to affect the pharmacokinetics of the drug product, enrollment of pediatric participants with infections other than the approved indication(s) in adult participants may be acceptable; in these situations, the investigational drug product is given in addition to SoC for the underlying infection. Sponsors should discuss their plans for study design and enrollment with the Agency.

— For multiple-dose PK and safety pediatric studies in which the investigational drug product is administered as the sole therapy, sponsors should limit enrollment of pediatric participants to the approved adult indication(s) or the adult indication(s) under investigation, provided there is preliminary evidence of safety and efficacy in adult participants. Sponsors should discuss their plans for study design and enrollment with the Agency.

— Sponsors should minimize the frequency of laboratory assessments to limit the number of invasive procedures and samples obtained for pediatric laboratory testing.

- Development of age-appropriate pediatric formulations, including considerations for palatability and acceptability of the drug product in children, is important. Sponsors must complete their pediatric assessments using age-appropriate formulations.[9]

- In general, pediatric doses of anti-infective drug products to be studied in clinical trials are selected based on exposure matching to adult participants. Modeling and simulation approaches can be used to select pediatric doses anticipated to provide similar exposure to adult participants. Additional clinical studies may be needed if there are uncertainties regarding the exposure-response relationship in pediatric and adult participants. More detailed information on clinical pharmacology considerations for neonatal and pediatric studies is provided in other guidances for industry.[10]

- Although most drug-drug interaction information[11] can be extrapolated from adult participants to pediatric participants, sponsors should consider common comorbidities in the intended pediatric population and whether additional drug-drug interaction information is needed.

- Juvenile toxicology studies:

  - The need for juvenile toxicology studies is based on the treatment indication, treatment duration, age of the pediatric population, safety data from adults, and other nonclinical studies (e.g., studies conducted in adult animals, pre- and postnatal development studies). The sponsor should provide a scientific justification regarding the plans for juvenile toxicology studies.

  - Examples of when FDA may recommend juvenile toxicology studies include, but are not limited to:

    - There are insufficient data from prior clinical experience, or safety concerns cannot be adequately addressed in other nonclinical studies.

    - The anti-infective drug product is intended primarily for a pediatric population. Depending on the proposed duration of the exposure in the pediatric population, FDA may also recommend long-term testing starting in juvenile animal toxicology studies.

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[9] Section 505B(a)(2)(A) of the FD&C Act and 21 U.S.C. 355c(a)(2)(A). See also section 505B(a)(4) of the FD&C Act. For further information, see the guidance for industry *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Initial Pediatric Study Plans* and the ICH guidances for industry *E11 Clinical Investigation of Medicinal Products in the Pediatric Population* and *E11(R1) Addendum: Clinical Investigation of Medicinal Products in the Pediatric Population*.

[10] See the draft guidances for industry *General Clinical Pharmacology Considerations for Neonatal Studies for Drugs and Biological Products* and *General Clinical Pharmacology Considerations for Pediatric Studies for Drugs and Biological Products*. When final, these guidances will represent the FDA's current thinking on these topics.

[11] See the guidance for industry *Clinical Drug Interaction Studies — Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions* (January 2020).

- Existing animal studies have identified a target organ or organs that undergo significant postnatal development during the expected clinical treatment duration and/or existing information regarding drug product pharmacology has identified a potential developmental concern (e.g., disrupted calcium signaling that could affect bone development).

— In general, FDA considers a study in juvenile animals from one relevant species, preferably rodent, to be adequate to evaluate toxicity endpoints for therapeutics that are well characterized in both adult humans and animals (a nonrodent juvenile species may be appropriate when scientifically justified).[12] Additional information on the nonclinical safety evaluation of pediatric drug products in juvenile animals can be found in other guidances for industry.[13, 14]

[12] We support the principles of the 3Rs (reduce/refine/replace) for animal use in testing when feasible. FDA encourages sponsors to consult with review divisions when considering a nonanimal testing method believed to be suitable, adequate, validated, and feasible. FDA will consider if the alternative method could be assessed for equivalency to an animal test method.

[13] See the ICH guidances for industry *S11 Nonclinical Safety Testing in Support of Development of Pediatric Pharmaceuticals* (May 2021) and *M3(R2) Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals* (January 2010) and the guidance for industry *Nonclinical Safety Evaluation of Pediatric Drug Products* (February 2006).

[14] For cellular or gene therapy products, see the guidance for industry *Preclinical Assessment of Investigational Cellular and Gene Therapy Products* (November 2013).