Development of Anti-Infective Drug Products for the Pediatric Population

Guidance for Industry

DRAFT GUIDANCE

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

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This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic.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 staff 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] for the pediatric population.

FDA encourages sponsors to discuss their initial pediatric study plans (iPSPs) for anti-infective drug products with the Agency early and, in most instances, 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. Additional information is available in several guidances for industry.[4] This guidance does not apply to preventative vaccines. Please note that the general principles set forth in this guidance apply to drugs and biologics. 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, and phage therapies), there may be additional development considerations. In such cases, CBER encourages sponsors to reach out to the applicable review division, as appropriate.

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[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 human drugs 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 the draft guidance for industry *Pediatric Study plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Initial Pediatric Study Plans* (March 2016). When final, this guidance will represent the FDA's current thinking on this topic. 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.

[4] 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.

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

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

- In addition to the effects of body size, developmental changes in neonates and young children, such as maturation of organ function and 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 older children and adults, may affect anti-infective drug 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 patients.

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 patients can be extrapolated to pediatric patients if:

    - The course of the infectious disease is similar in adult and the pediatric populations[5] (e.g., complicated intra-abdominal infections, complicated urinary tract infections, community-acquired bacterial pneumonia, and acute bacterial skin and structure infections). This implies a similar disease process, including the pathogens recovered from the site of infection.

    AND

[5] Section 505B(a)(2)(B)(i) of the Federal Food, Drug, and Cosmetic Act (FD&C Act).

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

Even when efficacy can be extrapolated, however, pediatric data will be needed 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 patients as in adult patients. Because the duration of most anti-infective treatments is usually short term, it may also be possible to obtain some information about clinical response to treatment in pediatric patients from these studies.

- Efficacy cannot be extrapolated from adult patients to pediatric patients, or one pediatric subpopulation to another for infections in which the pathophysiology and clinical manifestations of the disease are different between adult and pediatric patients or between the different pediatric population subgroups. For example, in immunocompetent older pediatric patients and adult patients, tuberculosis is predominantly a pulmonary disease; in pediatric patients younger than 2 years of age, however, tuberculosis can present as a more severe and disseminated disease including involvement of the central nervous system. Therefore, it would not be possible to extrapolate efficacy of a drug product studied only in older pediatric patients and adult patients for the treatment of tuberculosis to pediatric patients under 2 years of age.

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

- Age cohorts:

  – Cohorts for pediatric studies should be determined based on the incidence of the disease and any specific considerations for the drug product under evaluation. Sponsors can define cohorts based on criteria other than chronological age (e.g., weight-based criteria for oral drug products).

  – FDA encourages enrollment of some age cohorts in parallel for drug products that do not have specific safety concerns or pharmacokinetic properties that warrant a different approach. Sponsors should discuss such enrollment with the Agency.

  – Phase 3 clinical trials in adults could include adolescent patients (12 years and older) when there is sufficient safety data from adult patients to assess the risks and the prospect of direct benefit for the adolescent patients. Where appropriate from a

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

scientific and ethical perspective, FDA strongly encourages sponsors to enroll adolescent patients in adult trials.

- Safety data:

  - In general, safety data should be collected in all pediatric age ranges for which the drug product will be indicated, using the intended dose and duration of the drug product.

  - Safety data from adult clinical studies can provide supportive information and identify adverse events of interest for evaluation in pediatric studies.

  - The size of the recommended pediatric safety database of a drug product depends on several factors, such as the prevalence 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 on an ongoing basis as the clinical development of the drug product proceeds.

- 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 to identify pediatric patients for enrollment, such as duration of prior antibacterial therapy and choice of comparators based on standard of care at the enrolling site. Sponsors should discuss inclusion and exclusion criteria for enrollment in pediatric studies 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, depending upon the indication being studied.

  - In general, pediatric studies of anti-infective drug products use an active comparator that is considered standard of care at the study site and may include different comparators at different study sites.

  - Sponsors must complete their pediatric assessments using age-appropriate formulations,[7] and are expected to make these pediatric formulations available to patients. Sponsors who fail to seek approval for the pediatric formulations of their

[7] 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 draft guidance for industry *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Initial Pediatric Study Plans* (March 2016). When final, this guidance will represent the FDA's current thinking on this topic.

drug products will receive noncompliance letters, and their drug products may be considered misbranded and subject to relevant enforcement action.[8]

- In general, pediatric doses of anti-infective drug products to be studied in clinical trials are selected based on exposure matching to adult patients. Modeling and simulation approaches can be used to select pediatric doses anticipated to provide similar exposure to adult patients. Additional clinical studies may be needed if there are uncertainties regarding the exposure-response relationship in the pediatric and adult patients. Additional information on general clinical pharmacology considerations for neonatal and pediatric studies is provided in other guidances for industry.[9]

- Juvenile toxicology studies:

  - Juvenile toxicology studies are not required for anti-infective drug products before initiation of studies in pediatric patients in most instances. Treatment indication, treatment duration, age of the pediatric population, and safety data from adult patients and nonclinical studies can help determine the need for juvenile animal studies.

  - If juvenile toxicology studies are required, FDA generally 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).[10] Additional information on the nonclinical safety evaluation of pediatric drug products in juvenile animals can be found in other guidances for industry.[11,12]

[8] Section 505B(d) of the FD&C Act.

[9] 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.

[10] 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.

[11] See the International Council for Harmonisation guidance for industry *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).

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