Pediatric HIV Infection: Drug Development for Treatment

Guidance for Industry

DRAFT GUIDANCE

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For questions regarding this draft document, contact (CDER) Yodit Belew at 301-796-1500 or (CBER) Office of Communication, Outreach, and Development at 800-835-4709 or 240-402-8010.

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This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic.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 AND BACKGROUND

- This guidance provides general recommendations on the development of drug products for the treatment of human immunodeficiency virus (HIV) infection in pediatric patients (birth to younger than 17 years of age). This guidance is intended to help sponsors understand when it is appropriate to initiate pediatric formulation development and to begin pediatric studies to evaluate antiretroviral (ARV) drug products for the treatment of HIV infection.

- This guidance clarifies FDA's current thinking on critical aspects of the development of pediatric HIV drug products intended for global use. The guidance for industry *Human Immunodeficiency Virus-1 Infection: Developing Antiretroviral Drugs for Treatment* addresses the development of ARV drug products for the treatment of HIV infection.[2]

- This guidance does not address the full scope of considerations in the development program and clinical trial designs for ARV drug products to support an indication for the treatment of HIV-1 infection in adult or pediatric patients.[3]

[1] This guidance has been prepared by the Division of Antiviral Products in the Center for Drug Evaluation and Research, in cooperation with the Center for Biologics Evaluation and Research, at the Food and Drug Administration.

[2] 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/RegulatoryInformation/Guidances/default.htm.

[3] See the guidance for industry *Human Immunodeficiency Virus-1 Infection: Developing Antiretroviral Drugs for Treatment* and the draft guidance for industry *General Clinical Pharmacology Considerations for Pediatric Studies for Drugs and Biological Products*. 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/RegulatoryInformation/Guidances/default.htm.

- HIV infection is a chronic viral infection that, when untreated, causes a progressive destruction of the immune system resulting in acquired immunodeficiency syndrome (AIDS). Global data from the Joint United Nations Programme on HIV/AIDS (UNAIDS) indicate that approximately 2.1 million children (defined by UNAIDS as younger than 15 years of age) are living with HIV, of whom only 43% have received ARV therapy.[4] Treatment of HIV consists of a combination of ARV drug products, typically three drug products from at least two classes.

- The goal of treatment is to maintain suppression of plasma HIV ribonucleic acid (RNA) levels below the level of detection using sensitive HIV-RNA assays (less than the lower limit of quantification, target not detected). Because the course of HIV infection and the effects of ARV drug products are considered sufficiently similar in pediatric and adult patients, pediatric efficacy of ARV drug products is generally extrapolated from adult trials based on bridging pharmacokinetics.[5] In addition to pharmacokinetic data in children, safety and HIV-RNA (viral load) data to assess antiviral activity are collected during the pediatric studies.[6]

- 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. DRUG DEVELOPMENT CONSIDERATIONS

The following are the major considerations for sponsors developing pediatric HIV drugs intended for global use:

- Because dosing recommendations for ARV drug products have consistently been the same for adults and adolescents (for the purposes of this guidance 12 to younger than 17 years old),[7] sponsors should include adolescents in the initial efficacy (phase 3) trials

[4] UNAIDS, 2018, Fact Sheet — Latest Statistics on the Status of the AIDS Epidemics, UNAIDS.org, http://www.unaids.org/en/resources/fact-sheet.

[5] See the draft guidance for industry *General Clinical Pharmacology Considerations for Pediatric Studies for Drugs and Biological Products*. When final, this guidance will represent the FDA's current thinking on this topic.

[6] See the guidance for industry *Human Immunodeficiency Virus-1 Infection: Developing Antiretroviral Drugs for Treatment*.

[7] See the guidance for industry *Human Immunodeficiency Virus-1 Infection: Developing Antiretroviral Drugs for Treatment.*

along with adults, or a sponsor should conduct a separate adolescent study in parallel with the adult phase 3 trials.

- Pediatric formulation development should begin as soon as the adult dose is selected based on results from the phase 2 trial(s).

- For the nonadolescent pediatric population (for the purposes of this guidance age 4 weeks to less than 12 years),[8] sponsors should enroll cohorts within clinical studies in parallel rather than in series, unless a drug product has a specific safety or drug disposition factor that warrants a different approach. Sponsors can use pharmacokinetic modeling approaches using the adult and adolescent data for initial dose selection to initiate parallel enrollment of cohorts across the different weight groups in the nonadolescent pediatric population.[9]

- Cohort enrollment and dose selections during the nonadolescent pediatric clinical studies should be based on weight rather than age. The selected weight-bands should align with the weight-bands predefined by the World Health Organization (WHO).[10]

- Approval of a new pediatric formulation (e.g., granules instead of solution), when safety and pharmacokinetics in children have already been studied using a previously approved formulation, may be supported by a bioavailability/bioequivalence study in adults that show that bioavailability of the two formulations is comparable. If bioavailability in adults is not comparable, one or more of the following may be needed to support approval: dose adjustments, scientific rationale to support the difference in bioavailability, or an additional trial. Alternatively, additional work for the development of different formulations may be needed.

- FDA encourages sponsors to have early discussions with the WHO, nongovernmental organizations, FDA and others regarding pediatric plans to facilitate the development of drug products to meet the needs of pediatric patients (e.g., selection of formulation, strengths and dosage of a drug product).

[8] There may be circumstances in which evaluating ARV drugs for treatment in children younger than 4 weeks of age is appropriate and should be discussed with the Division of Antiviral Products.

[9] See the draft guidance for industry *General Clinical Pharmacology Considerations for Pediatric Studies for Drugs and Biological Products*. When final, this guidance will represent the FDA's current thinking on this topic.

[10] World Health Organization (WHO), 2016, Annex 11: Doses of Recommended Antiretroviral Drugs. In: WHO, Consolidated Guidelines on the Use of Antiretroviral Drugs for Treating and Preventing HIV Infection: Recommendations for a Public Health Approach, Second Edition, France: WHO, 388–395. Available at http://www.who.int/hiv/pub/arv/annexes-5Sep2016.pdf?ua=1.