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# **Pediatric HIV Infection: Drug Product Development for Treatment Guidance for Industry**

**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)**

**March 2019  
Clinical/Medical**

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## **Pediatric HIV Infection: Drug Product Development for Treatment Guidance for Industry<sup>1</sup>**

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 antiretroviral (ARV) drug products<sup>2</sup> for the treatment of human immunodeficiency virus (HIV) infection in pediatric (birth to younger than 18 years of age) patients. This guidance is intended to help sponsors understand when it is appropriate to initiate pediatric formulation development and to begin pediatric studies.

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* (November 2015) addresses more broadly the development of ARV drug products for the treatment of HIV infection.<sup>3</sup>

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.<sup>4</sup>

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<sup>1</sup> 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.

<sup>2</sup> For the purposes of this guidance, all references to *drug products* include both human drugs and biological products unless otherwise specified. The sponsor should discuss individual product differences with the Division of Antiviral Products during product development.

<sup>3</sup> 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>.

<sup>4</sup> 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* (December 2014). With respect to the latter, 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>.

## *Contains Nonbinding Recommendations*

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**

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 percent have received ARV therapy.<sup>5</sup> 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 by 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.<sup>6</sup> In addition to pharmacokinetic data in children, safety and HIV-RNA (viral load) data to assess antiviral activity are collected during the pediatric studies.<sup>7</sup>

## **III. DRUG PRODUCT DEVELOPMENT CONSIDERATIONS**

Following are the major considerations for sponsors developing pediatric HIV drug products 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 18 years of age),<sup>8</sup> the sponsor should include adolescents in the initial phase 3 (efficacy) clinical trials along with adults, or the sponsor should conduct a separate adolescent study in parallel with the adult phase 3 clinical trials. If adolescents are enrolled in an adult

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<sup>5</sup> UNAIDS, 2018, Fact Sheet—Latest Statistics on the Status of the AIDS Epidemics, UNAIDS.org, <http://www.unaids.org/en/resources/fact-sheet>.

<sup>6</sup> 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.

<sup>7</sup> See the guidance for industry *Human Immunodeficiency Virus-1 Infection: Developing Antiretroviral Drugs for Treatment*.

<sup>8</sup> See the guidance for industry *Human Immunodeficiency Virus-1 Infection: Developing Antiretroviral Drugs for Treatment*.

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phase 3 clinical trial, the sponsor should include them in the primary endpoint analysis. Differences between adolescents and adults, such as lower adherence rates, are not expected to affect clinical trial outcomes because the proportion of adolescents enrolled is expected to be comparatively small. The sponsor should also analyze the adolescent and the adult populations separately to help evaluate the consequences of possible differences in behaviors.

- The sponsor should begin pediatric formulation development 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, 4 weeks to younger than 12 years of age),<sup>9</sup> the sponsor 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. The sponsor can use pharmacokinetic modeling approaches based on the adult and the adolescent data for initial dose selection to initiate parallel enrollment of cohorts across the different weight groups in the nonadolescent pediatric population.<sup>10</sup>
- The sponsor should enroll neonates (birth to younger than 4 weeks of age) separately upon reviewing the pharmacokinetic data and establishing the dose(s) for the older pediatric cohorts.
- The sponsor should base cohort enrollment and dose selections during the nonadolescent pediatric clinical studies on weight rather than age. The selected weight bands should align with the weight bands predefined by the World Health Organization (WHO).<sup>11</sup>
- When the sponsor has already established dosing regimens in pediatric patients using a previously approved formulation, approval of a new pediatric formulation (e.g., granules instead of solution) can be supported by a relative bioavailability study in adults that shows that the bioavailability of the two formulations is comparable. If bioavailability in adults is not comparable, the sponsor can use one or more of the following to support approval of the new pediatric formulation: dose adjustments, scientific rationale supporting the acceptability of the difference in bioavailability, or an additional clinical trial. Alternatively, the sponsor can develop different formulations.

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<sup>9</sup> There may be circumstances in which evaluating ARV drug products for treatment in children younger than 4 weeks of age is appropriate and should be discussed with the Division of Antiviral Products.

<sup>10</sup> 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.

<sup>11</sup> 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>.

### *Contains Nonbinding Recommendations*

- The FDA encourages sponsors to have early discussions with the WHO, nongovernmental organizations, the 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, strength and dosage of a drug product).