Human Immunodeficiency Virus-1 Infection: Developing Systemic Drug Products for Pre-Exposure Prophylaxis

Guidance for Industry

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

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Clinical/Antimicrobial

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Contains Nonbinding Recommendations

Human Immunodeficiency Virus-1 Infection: Developing Systemic Drug Products for Pre-Exposure Prophylaxis 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 staff responsible for this guidance as listed on the title page.

I. INTRODUCTION

The purpose of this guidance is to provide to sponsors nonclinical and clinical recommendations specific to the development of systemic drug products, with a focus on long-acting systemic drug products (including small molecules and monoclonal antibodies), regulated within the Center for Drug Evaluation and Research at the Food and Drug Administration (FDA) for the prevention of sexually acquired human immunodeficiency virus-1 (HIV-1) infection. Specifically, this guidance addresses FDA's current thinking regarding the overall development program and clinical trial designs to support the development of systemic drug products for the prevention of HIV-1 infection. Investigational drug products for further development as pre-exposure prophylaxis (PrEP) can include the following: (1) an oral drug product approved for the treatment of HIV-1 infection that is subsequently developed as oral PrEP, (2) an oral drug product approved for the treatment of HIV-1 infection that is reformulated as a long-acting drug product or other delivery system (e.g., injectable, implantable device) for PrEP, or (3) a new investigational systemic drug product that is developed for treatment and/or prevention of HIV-1 infection.

This guidance does not address the development of vaginal microbicide drug products. That topic is discussed in the guidance for industry *Vaginal Microbicides: Development for the Prevention of HIV Infection* (November 2014) (vaginal microbicides guidance).[2] The following additional information can be found in the vaginal microbicides guidance: detailed nonclinical development, including in vitro virologic studies, specific information related to topical use and trials in female subjects, and more detailed information relating to protocol data collection and procedures. Except for the assessment of local microbicide effects, which are unique to vaginal microbicide development, the vaginal microbicides guidance is also generally applicable to the development of systemic drug products.

[1] This guidance has been prepared by the Division of Antiviral Products in the Center for Drug 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.

This guidance also does not discuss the general issues of statistical analysis or clinical trial design. Those topics are addressed in the ICH guidances for industry *E9 Statistical Principles for Clinical Trials* (September 1998) and *E10 Choice of Control Group and Related Issues in Clinical Trials* (May 2001), respectively.

FDA recognizes the challenges in evaluating systemic drug products for the prevention of sexually acquired HIV-1 infection. FDA continues to evaluate possible approaches for the development of new therapies for HIV prevention and will update this guidance if new information becomes available.

FDA encourages the sponsor considering development of systemic drug products for the prevention of HIV-1 infection to communicate with FDA through the preinvestigational new drug application consultation program.[3]

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. DEVELOPMENT CONSIDERATIONS

A. Nonclinical Considerations

Nonclinical virology considerations presented in the guidance for industry *Human Immunodeficiency Virus-1 Infection: Developing Antiretroviral Drugs for Treatment* (November 2015) are applicable to the development of systemic drug products for HIV-1 prophylaxis and should be reviewed.

Depending on the mechanism of action of some systemic drug products for HIV-1 prophylaxis, the sponsor should consider the potential of a drug to enhance HIV infectivity. For example, the sponsor should evaluate monoclonal antibodies for potential antibody-dependent enhancement of infection.

The sponsor can use animal models of HIV-1 infection (e.g., macaque/simian HIV rectal challenge models) to further support clinical development of systemic drug products (e.g., by determining threshold drug concentrations at which infection occurs to aid in initial dose selection or by exploring potentially effective drug combinations, delivery formulations, and dosing regimens).[4]

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[3] See the FDA web page Getting Started with the Division of Antiviral Products Pre-IND Process at https://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/InvestigationalNewDrugINDApplication/Overview/ucm077546.htm.

[4] 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

B. Clinical Pharmacology and Clinical Considerations for Long-Acting Systemic Drug Products

The sponsor can use an oral lead-in period (using an immediate-release formulation), if available, to achieve and maintain desired targeted drug concentrations and/or address early safety concerns before administering a long-acting systemic drug product. If an adverse reaction occurs during the lead-in period, an oral formulation allows for immediate withdrawal of an investigational systemic drug product, which is typically not feasible after a long-acting formulation has been dosed.

Long-acting systemic drug products can be developed in the absence of an immediate-release systemic drug product depending on the drug characteristics, including the known in vitro and in vivo safety profile of the systemic drug product and the potential for removal if formulated in an implantable device. For some drugs, an immediate release systemic drug product may not be feasible (e.g., monoclonal antibodies) or necessary (e.g., solid implant releasing systemic drug product with a short half-life).

In cases for which desired targeted drug concentrations are not expected to be reached for a considerable time period, the sponsor can consider other dosing strategies, such as the use of a loading dose (larger than the maintenance dose) or other maintenance dosing regimens.

Early in development, evaluation of the complete systemic concentration time course of the drug after the last administered dose is critical to assess the impact of residual drug concentrations on drug safety, development of resistance, and potential for continued drug interactions after stopping PrEP. In phase 1 multiple-dose studies, the sponsor should fully characterize the complete systemic concentration time course and collect blood samples for the measurement of drug concentration (pharmacokinetic (PK) samples) until the drug concentration is no longer detectable in plasma.

C. Dose Selection

The sponsor should use model-informed drug development approaches that leverage the available information (nonclinical and clinical) across the development program to inform dose selection whenever possible.

The sponsor should generally target systemic drug product exposures consistent with those of HIV-1 treatment (if available).

The sponsor can also select a dose or doses that result in exposures that are similar to or several fold higher than animal exposures that showed protection (if studies using animal models were conducted) if acceptable safety margins exist. Exposures below a known human HIV-1 treatment dose (if previously studied for treatment), but similar to animal model exposures that showed protection, may be acceptable for phase 2 and phase 3 clinical trials.

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suitable, adequate, validated, and feasible. FDA will consider if the alternative method could be assessed for equivalency to an animal test method.

In the absence of supportive clinical data or nonhuman primate data that showed protection, the sponsor may target systemic drug product exposures that are anticipated to exhibit antiviral activity (e.g., several fold above the cell culture protein-binding-adjusted EC_{90} value of the active moiety) if acceptable nonclinical safety margins exist.

D. Systemic Drug Product Characteristics That Affect End-User Acceptability

The effectiveness of any intervention for HIV-1 prevention is strongly correlated with user adherence. Therefore, subject adherence and subject retention in clinical trials are critical to the overall evaluation of safety and efficacy of an investigational systemic drug product. A systemic drug product with less frequent and more convenient dosing may be associated with greater adherence. Early in development, the sponsor should focus on systemic drug product characteristics (e.g., the number, frequency, and volume of injections; duration and characteristics of an implant) that might affect end-user adherence. The Division of Antiviral Products (DAVP) strongly encourages pretrial feasibility assessments to understand user preferences and to ensure systemic drug product attributes do not adversely affect subject adherence to a study regimen.

Data obtained in early development can guide systemic drug product reformulation, if needed, to optimize user acceptability before large-scale trials are started.

III. PHASE 3 CLINICAL TRIAL DESIGN FEATURES — KEY CONSIDERATIONS

A. Enrollment Criteria

The trial population should include healthy, non-HIV-infected sexually active adult men and women at substantial risk of acquiring HIV. Confirmation of HIV infection status before trial entry is critical, preferably by use of a diagnostic test that is sensitive to acute infection (e.g., capable of detecting HIV-1 RNA).

B. Trial Design

The sponsor should ensure that HIV prevention trials are randomized, double-blind, placebo-controlled trials or active-controlled superiority or noninferiority (NI) trials.[5] The sponsor should consider trial designs for the following populations:

- **Trials in men who have sex with men.** Trials should use an active control and can be either superiority trials or NI trials. The NI margin is determined using historical evidence of the treatment effect of an active control based on adequate and well-controlled superiority trials. Assumptions based on historical data, however, may be influenced by prior levels of adherence. The sponsor should consider these assumptions when estimating the HIV infection rate in subjects receiving an active control that is

[5] For trials in other high-risk adult populations (e.g., serodiscordant couples), the sponsor should discuss trial designs with DAVP.

based on historical data and should discuss the assumptions with DAVP prior to trial initiation. (Likewise, lack of treatment adherence or dropouts can affect the interpretation of prospective trial findings.)

- **Trials in high-risk women.** FDA recommends superiority designs because determination of an NI margin is difficult or impossible in this population because of the variable historical evidence of HIV prevention efficacy in at-risk women.

In general, two adequate and well-controlled trials are often needed to provide substantial evidence of effectiveness. However, the sponsor can consider evidence based on a single phase 3 trial acceptable if the results are robust with internal consistency, clinically and statistically persuasive, and supported by additional evidence (e.g., if the systemic drug product is already demonstrated to be effective for HIV treatment). If the sponsor is considering using a single-trial approach, the sponsor should discuss this with DAVP.

C. Efficacy Endpoint

The primary endpoint is the HIV infection rate per 100 person-years and is analyzed based on the intent-to-treat population, including all randomized subjects. The sponsor should not exclude subjects based on factors impacted by postrandomization selection.

The sponsor should follow all enrolled subjects for a minimum of 12 months and until the last enrolled subject completes the trial and the majority of subjects have received 24 months of follow-up.

D. Other Trial Features

The sponsor should submit for review a plan to assess adherence as part of the protocol and statistical analysis plan, and the sponsor should ensure that the plan includes objective methods, such as plasma drug levels, to provide estimates of drug product use over time. The sponsor should specify methods to document information on known factors that affect HIV transmission, such as condom usage and use of other prevention modalities. However, the sponsor should not adjust the primary analysis for actual use or compliance.

The Agency recommends the use of an FDA-approved HIV-1 RNA assay, when available, and the assay used should be specified in the clinical trial protocol. If the baseline/screening test does not use an HIV-1 RNA-specific assay or assays sensitive for acute infections, the sponsor should store baseline samples for retrospective HIV-1 RNA analysis (e.g., by RT-PCR) for all subjects. The sponsor should not consider retrospectively identified HIV-infected subjects missed by the screening assay prophylaxis failures and can exclude these subjects from the primary efficacy analysis.

Long-acting systemic drug products may persist for extended periods after systemic drug product discontinuation, potentially at concentrations too low for effective prophylaxis but high enough to select drug-resistant virus in case of acute infection. The sponsor should consider providing oral drugs for prophylaxis (e.g., emtricitabine/tenofovir DF) to subjects who discontinue a

systemic drug product with a long half-life and who are uninfected at the time of systemic drug product cessation but who remain at risk of HIV-1 infection. The sponsor should continue oral prophylaxis coverage until the investigational systemic drug product has been cleared. If oral prophylaxis coverage is deemed necessary, the sponsor should include these considerations in proposed labeling.

The sponsor should obtain PK samples from all subjects at trial visits at which HIV testing is performed and archive the samples for future analysis. The sponsor should record the time of previous doses and the time of sample collection for all PK samples. The sponsor should also analyze PK samples for subjects who seroconvert and compare the PK samples to those of a matched seronegative cohort.

The sponsor can use drug or drug metabolite concentration data to examine systemic drug product adherence.

Depending on the systemic drug product characteristics (e.g., if there is a device component for self-administration), the sponsor may need human factor and label comprehension studies to ensure labeling instructions for use are appropriate for the U.S. population. See the draft guidance for industry and FDA staff *Human Factor Studies and Related Clinical Study Considerations in Combination Product Design and Development* (February 2016).[6]

E. Specific Population Considerations

1. Pregnant Women[7]

Women who become pregnant during premarketing trials may be able to continue dosing; FDA's decision on a sponsor's proposal to dose pregnant women is made on a case-by-case basis and is dependent on the available data.[8]

Before considering including pregnant women in clinical trials, the sponsor should provide the following data. Findings from the toxicology studies should support the benefit-risk assessment to continue dosing in pregnant women.

- Completed reproductive toxicology studies, including data from fertility and early embryonic development studies, embryo-fetal development studies, and pre- and postnatal development studies

- Completed genotoxicity studies

[6] When final, this guidance will represent the FDA's current thinking on this topic.

[7] See the draft guidance for industry *Pregnant Women: Scientific and Ethical Considerations for Inclusion in Clinical Trials* (April 2018). When final, this guidance will represent the FDA's current thinking on this topic.

[8] See section III. A. 5. c., Safety in specific populations, of the vaginal microbicides guidance for more specific details on the types of data to be collected for women who become pregnant and continue dosing in clinical trials.

- Toxicity studies in two species to support the duration of exposure in human trials

2. Adolescents

The vaginal microbicides guidance outlines a two-stage approach for development of microbicides for use in adolescents, consisting of the collection of initial safety data from subjects 16 to 18 years old, followed by the recruitment of adolescents younger than 16 years old (depending on the clinical needs and pediatric research requirements of participating study sites). A two-stage approach may be appropriate for microbicide development given the potential differences in vaginal epithelial inflammation/toxicity and absorption within adolescent age groups. For systemic drug product development, the preferred approach for adolescents is enrollment in the adult clinical trials, or for the sponsor to conduct an adolescent study in parallel with the adult trials. The sponsor should make every effort to submit data from adolescents with the new drug application submission.

Extrapolation of efficacy from adults to adolescents is acceptable for systemic HIV drug products because acquisition of HIV infection in adolescents and the effects of systemic drug products are sufficiently similar between adult and adolescent populations. Therefore, after critical PK parameters for a systemic HIV drug product are identified from adult data, the adolescent development program can rely on matching the relevant adolescent and adult exposure parameters to demonstrate efficacy in the adolescent population. The sponsor should submit additional data to support safety in adolescents and to assess adherence.

The sponsor should collect supportive safety data in adolescents, unless the safety profile of the systemic drug product is already established in pediatrics.

Adherence data are important because lack of adherence could undermine the efficacy and safety of a systemic drug product in adolescents. Collection of usage data in adolescents is desirable until adolescent adherence is better understood for a given prevention modality (e.g., oral pill, injection). Once DAVP has reviewed usage and adherence information for a given prevention modality, the sponsor should discuss with DAVP the utility of the existing data to support use of a similar prevention modality (e.g., second oral systemic drug product seeking approval) and whether additional usage data are needed (e.g., if the dosing regimen differs).