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

Guidance for Industry

DRAFT GUIDANCE

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For questions regarding this draft document, contact Kimberly Struble, Pharm. D., at 301-796-1500.

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

June 2018
Clinical/Antimicrobial

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This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic.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 to sponsors nonclinical and clinical recommendations specific to the development of systemic drug products, with a focus on long-acting systemic drug products, 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 the 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 for PrEP; or (3) a new investigational drug product.

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* (vaginal microbicides guidance). The following additional information can be found in the vaginal microbicides guidance: detailed nonclinical development including in vitro virologic studies, developing drugs for topical use, specific information related to trials in female subjects, and more detailed information relating to protocol data collection and procedures. In general, the vaginal microbicides guidance also is applicable to the development of systemic drug products, except for the assessment of local microbicide effects that are unique to vaginal microbicide development.

[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.

This guidance also does not contain discussion of 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* and *E10 Choice of Control Group and Related Issues in Clinical Trials*, respectively.[2]

Sponsors considering development of drug products for the prevention of HIV-1 infection are encouraged to communicate with the FDA through the pre-investigational 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* 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, sponsors should consider the potential of a drug to enhance HIV infectivity. For example, sponsors should evaluate monoclonal antibodies for potential antibody-dependent enhancement of infection.

- Animal models of HIV-1 infection (e.g., macaque/SHIV rectal challenge models) can be used to further support clinical development (e.g., by determining threshold drug concentrations at which infection occurs to aid in initial dose selection or explore potentially effective drug combinations, delivery formulations, and dosing regimens).

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

- An oral lead-in (using an immediate-release formulation, if available) can be used to achieve and maintain desired targeted drug concentrations or address early safety

[2] We update guidances periodically. For 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 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.

concerns before administration of a long-acting formulation. If an adverse reaction occurs during the lead-in period, an oral formulation allows for immediate withdrawal of an investigational drug product, which is typically not feasible after a long-acting formulation has been dosed.

- Long-acting drug products can be developed in the absence of an immediate-release formulation (oral lead-in) depending on the drug characteristics, including the known in vitro and in vivo safety profile of the drug product.

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

- 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, sponsors should fully characterize the complete systemic concentration time course, with collection of blood samples for the measurement of drug concentration (pharmacokinetic (PK) samples) until the concentration is no longer detectable in plasma.

C. Dose Selection

- Sponsors 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.

- Sponsors should generally target systemic drug exposures consistent with those of HIV-1 treatment (if available) or target systemic drug exposures that are several-fold above the cell culture protein-binding-adjusted EC_{90} value.

- Sponsors can also select dose(s) 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.

D. Drug Product Characteristics That Affect End-User Acceptability

- The effectiveness of any intervention for HIV-1 prevention is strongly correlated with adherence. Therefore, subject adherence and retention are critical to the overall evaluation of safety and efficacy of an investigational drug product. A drug with less frequent and more convenient dosing may be associated with greater adherence. Early in development, sponsors should focus on drug product characteristics (such as the number, frequency, and volume of injections; duration and characteristics of an implant, among

others) that might affect end-user adherence. The Division of Antiviral Products (DAVP) strongly encourages pretrial feasibility assessments to understand user preferences and to ensure drug product attributes do not adversely affect subject ability to adhere to a study regimen.

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

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

- HIV prevention trials should be randomized, double-blind, placebo-controlled trials or active-controlled superiority or noninferiority (NI) trials.[4] Trials designs for the following populations should be considered.

  – **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 previous levels of adherence. These assumptions should be considered when estimating the HIV infection rate in subjects receiving an active control based on historical data. Likewise, interpretation of the trial findings can be affected by lack of treatment adherence or dropouts.

  – **Trials in high-risk women:** Superiority designs are recommended 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, evidence based on a single phase 3 trial can be considered acceptable if the results are statistically persuasive and supported by additional evidence (e.g., if the drug is already demonstrated to be effective for HIV treatment). If sponsors are considering using a single trial approach, they should discuss this with DAVP.

[4] For trials in other high-risk adult populations (e.g., serodiscordant couples), trial designs should be discussed with DAVP.

C. Efficacy Endpoint

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

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

D. Other Trial Features

- A plan to assess adherence should be submitted as part of the protocol and statistical analysis plan for review and should include: (1) objective methods, such as plasma drug levels to provide estimates of drug product use over time; and (2) methods to document information on known factors that affect HIV transmission, such as condom usage and use of other prevention modalities. However, the primary analysis should not be adjusted for actual use or compliance.

- If the baseline/screening test does not use an HIV-1 RNA-specific assay(s) sensitive for acute infections, baseline samples should be stored for retrospective HIV-1 RNA analysis (e.g., by RT-PCR) for all subjects. Retrospectively identified HIV-infected subjects missed by the screening assay should not be considered prophylaxis failures and can be excluded from the primary efficacy analysis.

- Long-acting antiretroviral drugs may persist for extended periods after drug product discontinuation, potentially at concentrations too low for effective prophylaxis but high enough to select drug-resistant virus in case of infection. Sponsors should consider providing oral drugs for prophylaxis (e.g., emtricitabine/tenofovir DF) to those subjects who discontinue a drug product with a long half-life, who are uninfected at the time of drug product cessation, but who remain at risk of HIV-1 infection. Oral prophylaxis coverage should continue until the investigational drug has been cleared. If oral prophylaxis coverage is deemed necessary, then these considerations should be included in the proposed labeling.

- PK samples should be obtained from all subjects at trial visits at which HIV testing is performed and the samples archived for future analysis. The time of previous doses and the time of sample collection should be recorded for all PK samples. PK samples for seroconverting subjects should be analyzed and compared to that of a matched seronegative cohort.

- Drug or drug metabolite concentration data can be used to examine drug product adherence.

- Depending on the drug product characteristics (e.g., if there is a device component for self-administration), human factor and label comprehension studies may be needed 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.*[5]

E. Specific Population Considerations

1. Pregnant Women

- Women who become pregnant during premarketing trials may be able to continue dosing; the 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.[6]

- Before inclusion of pregnant women in clinical trials can be considered, 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

  – 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 collection of initial safety data from subjects 16 to 18 years old, followed by recruitment of adolescents younger than 16 years (depending on the clinical needs and pediatric research requirements of participating trial 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 development, the preferred approach for adolescents is enrollment in the adult clinical trials, or for sponsors to conduct an adolescent trial in parallel with the adult trials. Sponsors should make every effort to submit data from adolescents with the new drug application submission.

- Adolescent extrapolation of efficacy is acceptable for systemic HIV prevention drug products because acquisition of HIV infection in adolescents and the effects of systemic drugs are sufficiently similar between adult and adolescent populations. Therefore, after

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

[6] 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.

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 effectiveness in the adolescent population. Additional data should be submitted to support safety in adolescents and to assess adherence.

- Sponsors should collect supportive safety data in adolescents, unless the safety profile of the drug product is already established in pediatrics.

- Adolescent adherence data are important because lack of adherence could undermine adolescent efficacy and safety. Collection of usage data in adolescents is desirable until adolescent adherence is better understood for a given prevention modality (e.g., pill, injection). After usage data are collected for a given prevention modality, sponsors should discuss with DAVP the utility of existing data to address adolescent adherence for a similar prevention modality (e.g., second oral drug product seeking approval) and whether additional usage data are needed (e.g., if the dosing regimen differs).