
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DRAFT GUIDANCE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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Food and Drug Administration
10001 New Hampshire Ave., Hillandale Bldg., 4th Floor
Silver Spring, MD 20993-0002*

*Phone: 855-543-3784 or 301-796-3400; Fax: 301-431-6353; Email: druginfo@fda.hhs.gov
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1 **Human Immunodeficiency Virus-1 Infection: Developing Systemic**
2 **Drug Products for Pre-Exposure Prophylaxis**
3 **Guidance for Industry¹**
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8 This draft guidance, when finalized, will represent the current thinking of the Food and Drug
9 Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not
10 binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the
11 applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible
12 for this guidance as listed on the title page.
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17 **I. INTRODUCTION**
18

19 The purpose of this guidance is to provide to sponsors nonclinical and clinical recommendations
20 specific to the development of systemic drug products, with a focus on long-acting systemic drug
21 products, regulated within the Center for Drug Evaluation and Research at the Food and Drug
22 Administration (FDA) for the prevention of sexually acquired human immunodeficiency virus-1
23 (HIV-1) infection. Specifically, this guidance addresses the FDA's current thinking regarding
24 the overall development program and clinical trial designs to support the development of
25 systemic drug products for the prevention of HIV-1 infection. Investigational drug products for
26 further development as pre-exposure prophylaxis (PrEP) can include the following: (1) an oral
27 drug product approved for the treatment of HIV-1 infection that is subsequently developed as
28 oral PrEP; (2) an oral drug product approved for the treatment of HIV-1 infection that is
29 reformulated as a long-acting drug product or other delivery system for PrEP; or (3) a new
30 investigational drug product.
31

32 This guidance does not address the development of vaginal microbicide drug products. That
33 topic is discussed in the guidance for industry *Vaginal Microbicides: Development for the*
34 *Prevention of HIV Infection* (vaginal microbicides guidance). The following additional
35 information can be found in the vaginal microbicides guidance: detailed nonclinical
36 development including in vitro virologic studies, developing drugs for topical use, specific
37 information related to trials in female subjects, and more detailed information relating to protocol
38 data collection and procedures. In general, the vaginal microbicides guidance also is applicable
39 to the development of systemic drug products, except for the assessment of local microbicide
40 effects that are unique to vaginal microbicide development.
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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.

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42 This guidance also does not contain discussion of the general issues of statistical analysis or
43 clinical trial design. Those topics are addressed in the ICH guidances for industry *E9 Statistical*
44 *Principles for Clinical Trials* and *E10 Choice of Control Group and Related Issues in Clinical*
45 *Trials*, respectively.²

46
47 Sponsors considering development of drug products for the prevention of HIV-1 infection are
48 encouraged to communicate with the FDA through the pre-investigational new drug application
49 consultation program.³

50
51 In general, FDA’s guidance documents do not establish legally enforceable responsibilities.
52 Instead, guidances describe the Agency’s current thinking on a topic and should be viewed only
53 as recommendations, unless specific regulatory or statutory requirements are cited. The use of
54 the word *should* in Agency guidances means that something is suggested or recommended, but
55 not required.

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II. DEVELOPMENT CONSIDERATIONS

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A. Nonclinical Considerations

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

66

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

71

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

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

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80 • An oral lead-in (using an immediate-release formulation, if available) can be used to
81 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>.

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

- 86
- 87 • Long-acting drug products can be developed in the absence of an immediate-release
88 formulation (oral lead-in) depending on the drug characteristics, including the known in
89 vitro and in vivo safety profile of the drug product.
- 90
- 91 • In cases where desired targeted drug concentrations are not expected to be reached for a
92 considerable period, sponsors can consider other dosing strategies such as the use of a
93 loading dose (larger than the maintenance dose).
- 94
- 95 • Early in development, evaluation of the complete systemic concentration time course of
96 the drug after the last administered dose is critical to assess the impact of residual drug
97 concentrations on drug safety, development of resistance, and potential for continued
98 drug interactions after stopping PrEP. In phase 1 multiple-dose studies, sponsors should
99 fully characterize the complete systemic concentration time course, with collection of
100 blood samples for the measurement of drug concentration (pharmacokinetic (PK)
101 samples) until the concentration is no longer detectable in plasma.
- 102

C. Dose Selection

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- 105 • Sponsors should use model-informed drug development approaches that leverage the
106 available information (nonclinical and clinical) across the development program to
107 inform dose selection whenever possible.
- 108
- 109 • Sponsors should generally target systemic drug exposures consistent with those of HIV-1
110 treatment (if available) or target systemic drug exposures that are several-fold above the
111 cell culture protein-binding-adjusted EC₉₀ value.
- 112
- 113 • Sponsors can also select dose(s) that result in exposures that are similar to or several-fold
114 higher than animal exposures that showed protection (if studies using animal models
115 were conducted), if acceptable safety margins exist. Exposures below a known human
116 HIV-1 treatment dose (if previously studied for treatment), but similar to animal model
117 exposures that showed protection, may be acceptable for phase 2 and phase 3 clinical
118 trials.
- 119

D. Drug Product Characteristics That Affect End-User Acceptability

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- 121
- 122 • The effectiveness of any intervention for HIV-1 prevention is strongly correlated with
123 adherence. Therefore, subject adherence and retention are critical to the overall
124 evaluation of safety and efficacy of an investigational drug product. A drug with less
125 frequent and more convenient dosing may be associated with greater adherence. Early in
126 development, sponsors should focus on drug product characteristics (such as the number,
127 frequency, and volume of injections; duration and characteristics of an implant, among

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128 others) that might affect end-user adherence. The Division of Antiviral Products (DAVP)
129 strongly encourages pretrial feasibility assessments to understand user preferences and to
130 ensure drug product attributes do not adversely affect subject ability to adhere to a study
131 regimen.
132

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

137 **III. PHASE 3 CLINICAL TRIAL DESIGN FEATURES — KEY CONSIDERATIONS**

138 **A. Enrollment Criteria**

- 139 • The trial population should include healthy, non-HIV-infected sexually active adult men
140 and women at substantial risk of acquiring HIV. Confirmation of HIV infection status
141 before trial entry is critical, preferably by use of a diagnostic test that is sensitive to acute
142 infection (e.g., capable of detecting HIV-1 RNA).
143
144

145 **B. Trial Design**

- 146 • HIV prevention trials should be randomized, double-blind, placebo-controlled trials or
147 active-controlled superiority or noninferiority (NI) trials.⁴ Trials designs for the
148 following populations should be considered.
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150
 - 151 – **Trials in men who have sex with men:** Trials should use an active control and can
152 be either superiority trials or NI trials. The NI margin is determined using historical
153 evidence of the treatment effect of an active control based on adequate and well-
154 controlled superiority trials. Assumptions based on historical data, however, may be
155 influenced by previous levels of adherence. These assumptions should be considered
156 when estimating the HIV infection rate in subjects receiving an active control based
157 on historical data. Likewise, interpretation of the trial findings can be affected by
158 lack of treatment adherence or dropouts.
 - 159 – **Trials in high-risk women:** Superiority designs are recommended because
160 determination of an NI margin is difficult or impossible in this population because of
161 the variable historical evidence of HIV prevention efficacy in at-risk women.
- 162 • In general, two adequate and well-controlled trials are often needed to provide substantial
163 evidence of effectiveness. However, evidence based on a single phase 3 trial can be
164 considered acceptable if the results are statistically persuasive and supported by
165 additional evidence (e.g., if the drug is already demonstrated to be effective for HIV
166 treatment). If sponsors are considering using a single trial approach, they should discuss
167 this with DAVP.
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⁴ For trials in other high-risk adult populations (e.g., serodiscordant couples), trial designs should be discussed with DAVP.

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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.

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216 • Depending on the drug product characteristics (e.g., if there is a device component for
217 self-administration), human factor and label comprehension studies may be needed to
218 ensure labeling instructions for use are appropriate for the U.S. population. See the draft
219 guidance for industry and FDA staff *Human Factor Studies and Related Clinical Study*
220 *Considerations in Combination Product Design and Development*.⁵

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E. Specific Population Considerations

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1. Pregnant Women

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2. Adolescents

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- 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.

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258 critical PK parameters for a systemic HIV drug product are identified from adult data, the
259 adolescent development program can rely on matching the relevant adolescent and adult
260 exposure parameters to demonstrate effectiveness in the adolescent population.
261 Additional data should be submitted to support safety in adolescents and to assess
262 adherence.

- 263
- 264 • Sponsors should collect supportive safety data in adolescents, unless the safety profile of
265 the drug product is already established in pediatrics.
 - 266 • Adolescent adherence data are important because lack of adherence could undermine
267 adolescent efficacy and safety. Collection of usage data in adolescents is desirable until
268 adolescent adherence is better understood for a given prevention modality (e.g., pill,
269 injection). After usage data are collected for a given prevention modality, sponsors
270 should discuss with DAVP the utility of existing data to address adolescent adherence for
271 a similar prevention modality (e.g., second oral drug product seeking approval) and
272 whether additional usage data are needed (e.g., if the dosing regimen differs).
273