# Fixed-Combinations and Single-Entity Versions of Previously Approved Antiretrovirals for the Treatment or Prevention of HIV-1 Under PEPFAR

## Guidance for Industry

***DRAFT GUIDANCE***

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For questions regarding this draft document, contact (CDER) Division of Antivirals at 301-796-1500.

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

**Procedural**
**August 2023**

**Revision 1**

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**U.S. Department of Health and Human Services**
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# Fixed-Combinations and Single-Entity Versions of Previously Approved Antiretrovirals for the Treatment or Prevention of HIV-1 Under PEPFAR
# Guidance for Industry[1]



## I. INTRODUCTION

This guidance provides recommendations for applications for single-entity (SE) antiretroviral (ARV) and fixed-combination (FC) ARV drug products for the treatment or prevention of human immunodeficiency virus-1 (HIV-1 or HIV) infection that are intended for distribution outside of the United States under the President's Emergency Plan for AIDS Relief (PEPFAR).[2] Specifically, this guidance addresses versions of previously approved SE and FC ARV drug products and FC ARV drug products for which the individual drug product components of the combination are already FDA-approved (i.e., for which substantial evidence of safety and efficacy of the specific individual drug product components or combination already exists).

This guidance discusses regulatory procedures relevant to such applications and makes recommendations on how to identify and address common issues.

This guidance revises the guidance for industry *Fixed Dose Combinations, Co-Packaged Drug Products, and Single-Entity Versions of Previously Approved Antiretrovirals for the Treatment of HIV* issued in October 2006. When finalized, this guidance will replace the October 2006 guidance. Significant changes from the 2006 final guidance include, but are not limited to, the following:

- Addition of information about ARV drug products for prevention of HIV infection.

[1] This guidance has been prepared by the Division of Antivirals (DAV) in cooperation with the Office of Pharmaceutical Quality, Office of Clinical Pharmacology, and Office of Generic Drugs (OGD) in the Center for Drug Evaluation and Research (CDER).

[2] For the purposes of this guidance, a *fixed-combination antiretroviral drug product* is one in which two or more antiretroviral drugs are combined in a single dosage form and the contribution of the individual drugs has been demonstrated to contribute to the effect(s) of the fixed-combination consistent with the requirements of 21 CFR 300.50. For the purposes of this guidance, the term *drug product* will be used to refer to human prescription drugs under section 505 of the Federal Food, Drug, and Cosmetic (FD&C) Act.

- Deletion of references to co-packaged products and focus on SE ARV and FC ARV drug products currently most needed under PEPFAR.

- Inclusion of a subsection that describes the processes for making changes to applications after tentative approval.

- Addition of updated descriptions of regulatory requirements and procedures in the main text of the guidance and deletion of Attachment A, which provided hypothetical scenarios.

- Reference to other FDA guidances for industry for common regulatory topics instead of repeating information.

- Addition of updated information in the section on chemistry, manufacturing, and controls to be consistent with other guidances for industry published after 2006.

- Deletion of Attachment B, which listed examples of two and three drug FCs supported by clinical data. Instead, the guidance refers applicants to a separate list[3] for ARV drug products supported by clinical data and needed for PEPFAR procurement. This list is published in conjunction with the FDA's PEPFAR database.

- Deletion of Attachment C, which listed combinations that were not acceptable for FC or co-packaging.

This guidance is not an exhaustive document on FDA's current thinking regarding the development and review of ARV drug products eligible for procurement under PEPFAR. Applicants can refer to other guidances cited in this document or seek advice from FDA when questions arise regarding specific drug development programs.

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.

[3] The separate list of ARV drug products, Antiretroviral Drug Products Needed for Use Under PEPFAR, can be found under question 6, What PEPFAR products can companies submit for FDA review?, at FDA's PEPFAR database on the Frequently Asked Questions web page available at https://www.fda.gov/international-programs/presidents-emergency-plan-aids-relief-pepfar/pepfar-database-frequently-asked-questions. This list is revised periodically to address current public health needs.

## II. BACKGROUND ON HIV TREATMENT, HIV PREVENTION, AND PEPFAR

### A. HIV Treatment

ARV drug products are essential for the treatment of HIV/AIDS (acquired immunodeficiency syndrome). The goals of HIV treatment are to maximally and durably suppress HIV to allow recovery of the immune system, reduce adverse clinical outcomes associated with HIV, reduce the emergence of resistance, and reduce HIV transmission to others. In the United States and developing countries, simplified HIV regimens in the form of FC ARV drug products improve patient adherence and facilitate distribution. For patients initiating ARV drug product therapy, preferred regimens are listed in the U.S. Department of Health and Human Services (DHHS) treatment guidelines,[4] the International AIDS Society guidelines,[5] and the World Health Organization (WHO) guidelines.[6]

### B. HIV Prevention

ARV drug products that are safe and effective for HIV prevention are important for people who are negative for HIV but are at substantial risk of HIV acquisition. The goal of using ARV drug products to prevent HIV acquisition is to reduce the morbidity, mortality, and cost to individuals and society associated with HIV infection. Recommendations for initiating HIV prevention, including recommended ARV drug products for prevention, are presented in the U.S. Public Health Service guidelines[7] and the WHO guidelines.[8]

### C. PEPFAR

PEPFAR is a U.S. Government initiative to help save the lives of those with HIV/AIDS around the world, outside the United States. It was originally announced in President George W. Bush's State of the Union address in 2003 and was reauthorized in 2008, 2013, and 2018. This historic

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[4] See the Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV developed by the DHHS Panel on Antiretroviral Guidelines for Adults and Adolescents – A Working Group of the Office of AIDS Research Advisory Council, available at https://clinicalinfo.hiv.gov/en/guidelines/hiv-clinical-guidelines-adult-and-adolescent-arv.

[5] See Saag MS, Benson CA, Gandhi RT, et al., 2018, Antiretroviral drugs for Treatment and Prevention of HIV Infection in Adults: 2018 Recommendations of the International Antiviral Society-USA Panel, JAMA, 320(4):379–396.

[6] See the WHO's Consolidated Guidelines on HIV Prevention, Testing, Treatment, Service Delivery and Monitoring: Recommendations for a Public Health Approach. Geneva: World Health Organization; 2021, available at https://www.who.int/publications/i/item/9789240031593.

[7] See the Centers for Disease Control and Prevention's U.S. Public Health Service: Preexposure Prophylaxis for the Prevention of HIV Infection in the United States — 2021 Update, available at https://www.cdc.gov/hiv/pdf/risk/prep/cdc-hiv-prep-guidelines-2021.pdf.

[8] See the WHO's Consolidated Guidelines on HIV Prevention, Testing, Treatment, Service Delivery, and Monitoring: Recommendations for a Public Health Approach, available at https://www.who.int/publications/i/item/9789240031593.

commitment is among the largest by any nation to combat a single disease internationally. As of 2012, ARV drug products are also available for HIV prevention, and as of 2015, WHO recommends the use of these drug products to reduce the risk of HIV acquisition. ARV drug products for treatment and more recently prevention play a major role in PEPFAR, and it is important that resources are spent on products that have been demonstrated to be safe and effective. ARV drug products for treatment or prevention of HIV must conform to regulatory standards of safety, efficacy, and quality[9] to maximize the success of treatment or prevention and to reduce the emergence and spread of resistant virus. Of note, FDA-approved or tentatively approved ARV drug products are eligible for procurement under PEPFAR.

### D. ARV Drug Products Needed for PEPFAR

The FDA's PEPFAR database[10] includes a list of ARV drug products that have been tentatively approved or approved and are eligible for procurement under PEPFAR, and a separate list[11] of ARV drug products that are currently most needed for HIV treatment or prevention in the developing world and countries supported by PEPFAR. An applicant should refer to the list of needed ARV drug products when considering submitting an ARV drug product application for HIV treatment and when evaluating whether to submit a user fee waiver request.[12] The list of needed ARV drug products for treatment is expected to evolve as HIV research continues and program needs change. An applicant that has access to data supporting the efficacy and safety of ARV drug products for treatment that are not included in the list of needed ARV drug products is encouraged to discuss with the Division of Antivirals (DAV)[13] its rationale for why the ARV drug product is important for PEPFAR and may qualify for a new drug application (NDA) user fee waiver. Similarly, an applicant is encouraged to consult DAV when considering submitting

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[9] Section 505 of the FD&C Act.

[10] The FDA's PEPFAR database is available at https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=pepfar.page.

[11] The separate list of ARV drug products, Antiretroviral Drug Products Needed for Use Under PEPFAR, can be found under question 6, What PEPFAR products can companies submit for FDA review?, at FDA's PEPFAR Database on the Frequently Asked Questions web page available at https://www.fda.gov/international-programs/presidents-emergency-plan-aids-relief-pepfar/pepfar-database-frequently-asked-questions. This list is revised periodically to address current public health needs.

[12] Under certain circumstances, FDA is authorized to waive user fees assessed under the Prescription Drug User Fee Act (PDUFA) for new drug applications (NDAs) and biological license applications (BLAs). In 2006, FDA issued a guidance for industry regarding certain user-fee waiver provisions of special relevance to PEPFAR products, *User Fee Waivers for FDC and Co-Packaged HIV Drugs for PEPFAR* (February 2007). In 2023, FDA published a new draft guidance for industry *PDUFA Waivers, Reductions, and Refunds for Fixed-Combinations and Single-Entity Versions of Previously Approved Antiretrovirals under PEPFAR* (August 2023). When final, the new user-fee guidance will replace FDA's 2006 guidance and 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/regulatory-information/search-fda-guidance-documents.

[13] For more information on contacting DAV, see the Office of Infectious Diseases web page at https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/office-new-drugs.

an ARV drug product application for HIV prevention and when evaluating whether to submit a user fee waiver request.[12]

## III. GENERAL CONSIDERATIONS

This guidance focuses on tentative approval of ARV drug products for HIV-1 treatment or prevention, particularly of those submitted in an abbreviated new drug application (ANDA) under section 505(j) of the Federal Food, Drug, and Cosmetic (FD&C) Act or in a section 505(b)(2) of the FD&C Act.[10,12] Because ARV drug products submitted as 505(b)(1) NDAs are usually eligible for approval rather than tentative approval, these applications are generally not discussed in this guidance.

A tentative approval may be granted for ARV drug products that cannot be marketed in the United States because of existing patents and/or exclusivity.[14] Drug products that receive tentative approval meet the same substantive requirements (e.g., safety, efficacy, and quality standards) as drug products that receive final marketing approval.

FDA will not grant a tentative approval action in lieu of final marketing approval when there are no patent and exclusivity barriers to final approval.[15]

### A. Submitting ARV Drug Product Applications Eligible for Procurement Under PEPFAR Through the Appropriate Abbreviated Approval Pathway

An applicant should determine whether its application should be submitted as an ANDA or a 505(b)(2) NDA as discussed briefly in this section and as addressed in detail in the guidance for industry *Determining Whether to Submit an ANDA or a 505(b)(2) Application* (May 2019).[16] That guidance highlights statutory and regulatory criteria for submitting applications under the abbreviated approval pathways described in section 505(j) and 505(b)(2) of the FD&C Act, identifies considerations to help potential applicants determine which pathway is most appropriate, and provides recommendations to potential applicants on requesting assistance from FDA in making this determination.

#### *1. ANDAs*

Like all ANDAs, an ANDA for an ARV drug product is submitted and approved under section 505(j) of the FD&C Act (commonly referred to as a *generic* drug application). An ANDA relies on FDA's finding that the previously approved drug product, i.e., the reference listed drug

[14] See 21 CFR 314.3(b) and 21 CFR 314.105. If one or more active moiety in an ARV drug product is protected by new chemical entity exclusivity, acceptance of an ANDA or 505(b)(2) NDA containing that active moiety for review could be delayed. See sections 505(c)(3)(E)(ii) and 505(j)(5)(F)(ii) of the FD&C Act; 21 CFR 314.108(b).

[15] See 21 CFR 314.105.

[16] We update guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

(RLD), is safe and effective. An RLD is defined as the listed drug identified by FDA as the drug product upon which an applicant relies in seeking approval of its ANDA[17] and is listed in the FDA's Approved Drug Products with Therapeutic Equivalence Evaluations (commonly known as the Orange Book).[18] An ANDA generally must contain information to show that the proposed drug product (1) is the same as the RLD with respect to the active ingredient(s), conditions of use, dosage form, strength, route of administration, and labeling (with certain permissible differences), and (2) is bioequivalent to the RLD.[19] FDA's review process ensures that generic drug products perform the same way in the human body and have the same intended use as the RLD. All generic drug products approved by FDA have the same high quality, strength, purity, and stability as brand-name drug products. In addition, FDA inspects facilities to make certain the generic manufacturing, packaging, and testing sites pass the same quality standards as those of brand-name drug products.

ANDAs are reviewed in FDA's Office of Generic Drugs (OGD). If an applicant has questions about its proposed ARV drug product, the applicant can submit a controlled correspondence to FDA's OGD.[20]

*2. 505(b)(2) NDAs*

A 505(b)(2) NDA for an SE or FC ARV drug product must contain full reports of investigations of safety and effectiveness, where at least some of the information required for approval comes from studies not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use[21] (e.g., the Agency's finding of safety and/or effectiveness for a listed drug, published literature). A 505(b)(2) NDA applicant may rely on FDA's finding of safety and/or effectiveness for a listed drug only to the extent that the proposed product in the 505(b)(2) application shares characteristics (e.g., active ingredient, dosage form, route of administration, strength, indication or other conditions of use) in common with the relied-upon listed drug(s). The applicant is expected to establish a *bridge* (e.g., by using comparative bioavailability data) between the proposed drug product and each listed drug that the applicant seeks to rely upon to demonstrate that reliance on the listed drug is scientifically justified. To the extent that the listed drug and the drug proposed in the 505(b)(2) NDA differ (e.g., a product with a different dosage

[17] 21 CFR 314.3(b). See also the guidance for industry *Referencing Approved Drug Products in ANDA Submissions* (October 2020).

[18] Available at https://www.fda.gov/drugs/drug-approvals-and-databases/approved-drug-products-therapeutic-equivalence-evaluations-orange-book.

[19] See section 505(j)(2) and 505(j)(4) of the FD&C Act; 21 CFR 314.94, 21 CFR 314.127, and 21 CFR 320.21(b). See also the guidance for industry *Determining Whether to Submit an ANDA or a 505(b)(2) Application*.

[20] See the draft guidance for industry *Controlled Correspondence Related to Generic Drug Development* (December 2022) for information on the types of inquiries appropriate for controlled correspondence and on how to submit controlled correspondence to OGD. When final, this guidance will represent the FDA's current thinking on this topic.

[21] See 21 CFR 314.3(b).

form or a product that is intentionally more bioavailable than the listed drug), the 505(b)(2) NDA must include sufficient data to support those differences.[22] For drug products included in the list of needed drug products[23] on the FDA's PEPFAR database,[24] submission of a 505(b)(2) NDA that relies on FDA's findings of safety and effectiveness for approved SE or FC ARV drug products may be appropriate if the applicant does not have a right of reference to data establishing the safety and efficacy of the SE or FC ARV drug product.

505(b)(2) NDAs for ARV drug products are reviewed in DAV, which is part of FDA's Office of New Drugs.[25] If an applicant has questions about submission of an application through the 505(b)(2) pathway, the applicant should contact DAV for assistance.

## B. Changes Made After Tentative Approval of an Application

An applicant can submit amendments to a tentatively approved application that propose changes to the application, request final approval, or both propose changes and request final approval. This section describes appropriate data to submit in an amendment to the application when changes (including significant changes, e.g., addition of new manufacturing sites or important new safety information) are made after tentative approval, but before final marketing approval.

### *1. Amendments: Before Final Marketing Approval Request*

While a drug product that is granted tentative approval is not an approved drug and may not be marketed in the United States until final approval,[26] a tentatively approved ANDA or NDA for an ARV drug product may be eligible for procurement and distribution outside the United States under PEPFAR. Accordingly, an applicant may determine that changes (e.g., manufacturing, labeling) to its tentatively approved application eligible for procurement under PEPFAR may be appropriate or necessary as a scientific matter. In general, these changes are processed as amendments to tentatively approved applications. Although the administrative and regulatory procedures for handling changes to these tentatively approved applications may differ from the procedures for changes to ANDAs and NDAs after final approval, the scientific principles that guide the evaluation of these changes generally remain the same. In other words, FDA considers

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[22] See 21 CFR 314.93.

[23] The separate list of ARV drug products, Antiretroviral Drug Products Needed for Use Under PEPFAR, can be found under question 6, What PEPFAR products can companies submit for FDA review?, at FDA's PEPFAR Database on the Frequently Asked Questions web page available at https://www.fda.gov/international-programs/presidents-emergency-plan-aids-relief-pepfar/pepfar-database-frequently-asked-questions. This list is revised periodically to address current public health needs.

[24] The FDA's PEPFAR database is available at https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=pepfar.page.

[25] For guidance on the content and format of or the submission process for an NDA, see the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents and search using the term *NDA* and select either the Administrative/Procedural or Clinical/Medical topic in the filter.

[26] See 21 CFR 314.3(b) and 21 CFR 314.105. See also 505(j)(5)(B)(iv)(II)(dd) of the FD&C Act.

the assessment of risk and type of change for such ANDA and NDA amendments similarly to supplements to approved applications. Therefore, when proposing changes to these tentatively approved applications, FDA recommends that an applicant indicate in a cover letter its view of whether the changes are considered a major, moderate, or minor potential to have an adverse effect on the quality of the drug product. FDA expects to review PEPFAR change amendments for tentatively approved NDAs as shown in the timelines in Table 1. FDA classifies amendments to tentatively approved ANDAs as unsolicited, and in general, FDA will set a review goal consistent with the recommendations outlined in section IV of the guidance for industry *ANDA Submissions—Amendments to Abbreviated New Drug Applications Under GDUFA* (July 2018) (see Table 2).

**Table 1. Types of PEPFAR Change Amendments and Review Timelines for Tentatively Approved NDAs** [*]

| | **Type of Change** | **FDA Review Timelines** | **Change Amendment Implementation** | |
|---|---|---|---|---|
| | Amendment – Major Change | 4 months | Requires submission of change and decisional action by FDA before implementation | |
| | Amendment – Moderate Change | 6 months | Requires submission of change, but the change can be implemented 30 days after FDA officially receives the submission | |
| | Amendment – Minor Change[a] | 6 months | | |

PEPFAR = President's Emergency Plan for AIDS Relief; NDA = new drug application.

[a] Includes changes that, for approved applications, would be submitted in annual reports per 21 CFR 314.70(d).

**Table 2. Review Performance Goals for ANDA* Amendments[27]**

| Submission Type | Goal |
|---|---|
| **Standard Major ANDA Amendments** | 90% within 8 months of submission date if preapproval inspection not required |
| | 90% within 10 months of submission date if preapproval inspection required |
| **Priority Major ANDA Amendments** | 90% within 6 months of submission date if preapproval inspection not required |
| | 90% within 8 months of submission date if preapproval inspection required and applicant meets requirements described in the GDUFA III Commitment Letter[b] |
| | 90% within 10 months of submission date if preapproval inspection required and applicant meets limitations described in the GDUFA III Commitment Letter[b] |
| **Standard Minor and Priority Minor[a] ANDA Amendments[a]** | 90% within 3 months of submission date |

* ANDA = abbreviated new drug application.
[a] Includes changes to ANDAs for ARV drug products eligible for procurement under PEPFAR that are recommended as moderate type change amendments.
[b] See the Generic Drugs User Fee Act (GDUFA) Reauthorization Performance Goals and Program Enhancement Fiscal Years 2023–2027 https://www.fda.gov/industry/generic-drug-user-fee-amendments/gdufa-iii-reauthorization.

To make a risk assessment of a proposed change amendment (e.g., determine whether a change has a major, moderate, or a minor potential to have an adverse effect on the identity, strength, quality, purity, or potency of the drug product) and to determine what information or data should be submitted to support the proposed change amendment, FDA recommends that applicants refer to the following guidances for industry:

- *Changes to an Approved NDA or ANDA* (April 2004)
- *Changes to an Approved NDA or ANDA: Questions and Answers* (January 2001)
- *Immediate-Release Solid Oral Dosage Forms: Scale-Up and Postapproval Changes: Chemistry, Manufacturing, and Controls, In Vitro Dissolution Testing, and In Vivo Bioequivalence Documentation* (November 1995)
- *PAC-ATLS: Postapproval Changes — Analytical Testing Laboratory Sites* (April 1998)

After review of a change amendment for an NDA or an ANDA, FDA generally sends the applicant one of two types of notifications noted below. In either case, the original application remains tentatively approved.

[27] See the guidance for industry *ANDA Submissions—Amendments to Abbreviated New Drug Applications Under GDUFA*. Note that review goal percentages refer to all ANDAs, not just those for drug products eligible for procurement under PEPFAR.

The possible types of notifications are:

- A PEPFAR Permitted letter, if the change is found acceptable
- A PEPFAR Denied letter, if the change is found unacceptable

Implementation of a change submitted as a minor or moderate change amendment before issuance of a PEPFAR Permitted letter is at the risk of the applicant. If FDA determines that a change submitted as a minor or moderate change amendment is a major change amendment, FDA will notify the applicant not to implement the change until a PEPFAR Permitted letter is issued for the major change to the tentatively approved application.

For approved applications, applicants must submit postmarketing reports (e.g., annual reports);[28] although this requirement does not apply to tentatively approved applications, FDA recommends that applicants submit information related to the distribution outside the United States under PEPFAR of a product described in a tentatively approved ANDA or NDA as an amendment designating the information as an *annual update*. An annual update provides the FDA reviewer with background information that may be useful in reviewing other changes to the application. Information that is useful in an annual update includes distribution data, stability updates (e.g., on original registration batches, commitment batches, and annual batches), a copy of the current labeling (including a representative container label), and a cumulative list of all change amendments submitted through amendments after tentative approval.

Recommended format for the cumulative list of change amendments with their current statuses (e.g., pending, permitted, denied) can be found in the guidance for industry *Format and Content for the CMC Section of an Annual Report* (September 1994).

See section VI.E., CMC Changes After a Tentative Approval, for examples of changes to tentatively approved applications.

#### *2. Amendments: Requesting Final Approval*

When the period of patent and exclusivity protection is ending or has ended, the applicant may submit an amendment to a tentatively approved application requesting final approval. The amendment should include final labels and labeling that comply with all applicable U.S. regulations (e.g., uniqueness of drug product appearance in accordance with 21 CFR part 206; child-resistant packaging in accordance with 16 CFR part 1700).[29] The amendment should also

[28] 21 CFR 314.81.

[29] In addition, for ANDAs, if the prescribing information includes reference to the antiretroviral pregnancy registry contact number, then the prescribing information for the generic product must also include the same antiretroviral pregnancy registry reference. See, for example, section 505(j)(4)(G) of the FD&C Act; 21 CFR 314.127(a)(7). Including the pregnancy registry contact in the prescribing information means that a sponsor has joined the antiretroviral pregnancy registry. For 505(b)(2) NDAs, the need to include a reference to the antiretroviral pregnancy registry will be decided on a case-by-case basis depending on what is known about the risk and benefit of the use of the ARV drug(s) in pregnant females.

either describe all significant changes to the drug product and manufacturing processes made since tentative approval or certify that no significant changes have been made. A guidance for industry is available that provides recommendations for seeking final approval of tentatively approved ANDAs.[30]

### C. Regulatory Procedures that May Expedite the Availability of ARV Drug Products Submitted in NDAs Eligible for Procurement Under PEPFAR[31]

To facilitate rapid development and review of NDAs for ARV drug products eligible for procurement under PEPFAR, DAV interacts with applicants early in the development stages to discuss the appropriateness of the SE or FC ARV drug product, the dosing strength, and the appropriate nonclinical and chemistry, manufacturing, and controls (CMC) data. In addition, some of the regulatory procedures for expediting review of NDAs may apply to ARV NDAs, such as fast track designation and priority review designation. Applicants should refer to FDA's guidance for industry *Expedited Programs for Serious Conditions — Drugs and Biologics* (May 2014) for more information on these expedited programs.

## IV. CLINICAL CONSIDERATIONS

FDA believes adequate clinical studies confirming safety and efficacy have already been conducted for ARV drug products needed for PEPFAR and listed on the FDA's PEPFAR database;[32] therefore, in general, new clinical studies are not needed to support applications for these drug products when the doses of the approved ARV drug products are unchanged.

Proposed SE and FC ARV drug products should be relatively well tolerated and easy to administer, provide potency and a barrier to the emergence of drug resistance, and have available clinical safety and efficacy data that support use of the drug product. Proposed FC ARV drug products for HIV treatment intended to be eligible for procurement under PEPFAR should contain two or more components of an established fully suppressive ARV regimen that are recommended as a preferred or alternative regimen (or regimen component) for treatment-naïve patients with HIV in treatment guidelines.[33] Proposed ARV drug products for HIV prevention

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[30] See the guidance for industry *ANDA Submissions — Amendments and Requests for Final Approval to Tentatively Approved ANDAs* (September 2020).

[31] These approaches do not apply to potential ANDA submissions.

[32] The FDA's PEPFAR database is available at https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=pepfar.page. In general, SE and FC ARV drug products listed on the FDA's PEPFAR database were evaluated in at least one study conducted under good clinical practices that evaluated changes in HIV-RNA and $CD_4$ cell counts for at least 48 weeks and showed statistical noninferiority, or superiority, of the ARV drug product or regimen to an accepted control at the time the study was conducted.

[33] See the Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV developed by the DHHS Panel on Antiretroviral Guidelines for Adults and Adolescents – A Working Group of the Office of AIDS Research Advisory Council, available at https://clinicalinfo.hiv.gov/en/guidelines; and the WHO's Consolidated

eligible for procurement under PEPFAR should represent a prevention option as recommended in treatment guidelines.[34]

Proposed drug products that change the dose of an approved ARV drug product could, as a scientific matter, need additional clinical studies to support the change as compared to the relied upon listed drug. Potential applicants should request advice from DAV in this situation.

### A. Pediatric Considerations

FDA encourages applicants to review consensus pediatric guidelines and focus development efforts on the types of drug products most needed. Drug products distributed under PEPFAR are used in some countries where liquid drug products may pose significant challenges. Families with pediatric patients may travel long distances to and from a clinic making it difficult to transport bulky, heavy bottles of liquid medication. Many families may not have a place to store liquid formulations, particularly if refrigeration is required. Thus, alternative suitable pediatric formulations are preferred, such as tablets for oral suspension or oral pellets that can be mixed with food. To allow maximum flexibility in dosing, another desirable dosage form is a scored tablet that can be crushed and dispersed in liquid or food vehicle if the patient cannot swallow a solid dosage form. Scored tablets can include a single score that bisects the tablet or multiple score lines, allowing the tablets to be divided into halves, thirds, and/or quarters. Applicants should refer to the guidance for industry *Tablet Scoring: Nomenclature, Labeling, and Data for Evaluation* (March 2013).

Dosing instructions for ARV drug products intended for pediatric patients typically include dosing recommendations by weight band. For FC ARV drug products submitted as a 505(b)(2) NDA, it may not be possible to match the U.S. approved dose for each component across all weight bands. If the application proposes doses for weight bands that differ from such previously approved doses, the safety and efficacy of such proposed doses at the limits of weight bands should be supported by clinical study data or scientific literature. Potential applicants should request advice from DAV in this situation.

## V. CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS

This section describes the types of clinical pharmacology and biopharmaceutical data that are particularly relevant for ARV drug products eligible for procurement under PEPFAR. For additional details, applicants should refer to other guidances for industry cited in this section.

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Guidelines on HIV Prevention, Testing, Treatment, Service Delivery and Monitoring: Recommendations for a Public Health Approach, available at https://www.who.int/publications/i/item/9789240031593.

[34] See the Centers for Disease Control and Prevention's U.S. Public Health Service: Preexposure Prophylaxis for the Prevention of HIV Infection in the United States — 2021 Update, available at https://www.cdc.gov/hiv/pdf/risk/prep/cdc-hiv-prep-guidelines-2021.pdf.

### A. Bioequivalence or Bioavailability Studies[35]

Bioequivalence or bioavailability studies are needed to bridge FDA's finding of safety and efficacy of U.S. approved drug products to the PEPFAR drug product.

For a drug product submitted in an ANDA (under section 505(j) of the FD&C Act), applicants must demonstrate that their drug product is bioequivalent to the RLD. In addition, applicants must use the reference standard (RS), which is selected by FDA, in conducting any in vivo bioequivalence testing required to support approval.[36] The RLD and RS are identified in the Orange Book. Applicants should refer to the guidance for industry *Referencing Approved Drug Products in ANDA Submissions* and the draft guidance for industry *Bioequivalence Studies With Pharmacokinetic Endpoints for Drugs Submitted Under an ANDA* (August 2021).[37] For additional information on recommended bioequivalence studies to support submission of a particular drug product, ANDA applicants can also access the OGD web page, Product-Specific Guidances for Generic Drug Development, available at: https://www.accessdata.fda.gov/scripts/cder/psg/index.cfm.

For an SE or FC ARV drug product submitted as an NDA (under section 505(b)(2) of the FD&C Act), a relative bioavailability study or studies may be necessary as a scientific matter. Applicants should refer to the guidance for industry *Bioavailability Studies Submitted in NDAs or INDs — General Considerations* (April 2022).

All bioanalytical methods should be well characterized, fully validated, and documented. For additional details, applicants should refer to the guidance for industry *Bioanalytical Method Validation* (May 2018).

### B. Assessment of the Effect of Food

It is important to evaluate the effect of food on the absorption of the active ingredients of the ARV drug products eligible for procurement under PEPFAR.

For ARV drug products submitted under the ANDA pathway (section 505(j) of the FD&C Act), applicants should refer to the Product-Specific Guidances for Generic Drug Development resources[38] and the draft guidance for industry *Bioequivalence Studies With Pharmacokinetic Endpoints for Drugs Submitted Under an ANDA.*[39]

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[35] See generally 21 CFR part 320, Bioavailability and Bioequivalence Requirements.

[36] See 21 CFR 314.3(b).

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

[38] Available at https://www.fda.gov/drugs/guidances-drugs/product-specific-guidances-generic-drug-development.

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

For ARV drug products submitted under the 505(b)(2) NDA pathway), applicants should refer to the draft guidance for industry *Assessing the Effects of Food on Drugs in INDs and NDAs — Clinical Pharmacology Considerations* (February 2019)[40] and guidance for industry *Bioavailability Studies Submitted in NDAs or INDs — General Considerations*.

### C. Waivers of Bioequivalence or Bioavailability Studies

There are circumstances in which an in vivo bioequivalence or bioavailability study can be waived.[41] For FDA's current thinking on such waivers, applicants should refer to the following guidances for industry:

Draft guidances[42]

- *Bioequivalence Studies With Pharmacokinetic Endpoints for Drugs Submitted Under an ANDA*
- *Bioavailability Studies Submitted in NDAs or INDs — General Considerations*

Final guidances

- *M9 Biopharmaceutics Classification System-Based Biowaivers* (May 2021)
- *Dissolution Testing of Immediate Release Solid Oral Dosage Forms* (August 1997)
- *Dissolution Testing and Acceptance Criteria for Immediate-Release Solid Oral Dosage Form Drug Products Containing High Solubility Drug Substances* (August 2018)

### D. Pediatric Formulations

Results from bioavailability studies should be included in NDA submissions supporting pediatric formulations. Bioavailability studies, which are typically conducted in adult patients, should evaluate the drug product administered under conditions described in the proposed product labeling (e.g., chewed, crushed, dissolved, dispersed, or sprinkled in an appropriate liquid or food vehicle[43]). In some cases, additional administration conditions may need to be evaluated.

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

[41] See, for example, 21 CFR 320.21 and 21 CFR 320.22.

[42] When final, these guidances will represent the FDA's current thinking on these topics.

[43] See the draft guidance for industry *Use of Liquids and/or Soft Foods as Vehicles for Drug Administration: General Considerations for Selection and In Vitro Methods for Product Quality Assessments* (July 2018). When final, this guidance will represent the FDA's current thinking on this topic.

# VI. CHEMISTRY, MANUFACTURING, AND CONTROLS

This section highlights certain specific topics with respect to CMC submissions in ANDAs and NDAs for ARV drug products eligible for procurement under PEPFAR. Applicants should refer to other guidances for industry cited in this section for additional details on FDA's current thinking regarding submission of CMC information.

## A. Drug Master Files

Drug substance manufacturing processes should be well-documented through reference to drug master files (DMFs) of the drug substance manufacturers, if complete data cannot be included in the application. Applicants should ensure that DMFs are submitted to FDA for the processes used in the manufacturing of the drug substance(s) for both the registration batches of the drug product and for the intended commercial drug product.
If reference is made to a DMF, applicants should ensure that the DMF is submitted to FDA and that a Letter of Authorization to refer to this DMF is included in the NDA or ANDA and in the DMF itself.[44]

A single DMF may have multiple manufacturing sites, and each site should be listed in the ANDA or NDA even though the DMF number is the same. Applicants should clarify which of the drug substance manufacturing sites in the DMF will be used to produce drug substance(s) for the drug product. Asking DMF holders, before the ANDA/NDA submission, about any changes planned for the near future may lessen the need for late change amendments to the ANDA or NDA.

When a DMF is changed, the DMF holder should notify applicants to whom Letters of Authorization have been issued. These applicants should submit the appropriate amendment to their application(s) that reference this DMF. For example, notification of a new manufacturing site is generally a major change amendment and can extend the review goal accordingly, particularly if an inspection is needed.[45] When notified of a new manufacturing site by a DMF holder during a review cycle, the applicant should contact the regulatory project manager in either OND or OGD and the regulatory business project manager in the Office of Pharmaceutical Quality immediately.

## B. Manufacturing Facilities and Processes

All facilities used in the manufacturing, testing, packaging, and labeling of the drug substance(s) and the drug product are subject to inspection and should be ready and available for inspection before approval to assess compliance with current good manufacturing practice.[46]

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[44] See 21 CFR 314.420 for additional information on referencing DMFs.

[45] See 21 CFR 314.60(b). See also section III.B.1., Amendments: Before Final Marketing Approval Request, and 21 CFR 314.70(b).

[46] See 21 U.S.C. 351(a)(2)(B), 21 CFR parts 210 and 211. See also, guidance for industry *Q7 Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients* (September 2016).

The process activities, including actual protocols, sampling plans, and acceptance criteria as well as study outcomes, will be evaluated during a current good manufacturing practice inspection. Process validation should be complete before the release of the drug product intended for distribution. Applicants should refer to the guidance for industry *Process Validation: General Principles and Practices* (January 2011).

## C. Drug Substance Issues

Scientific issues related to controls and impurities may arise during FDA review of ARV drug product submissions intended to be eligible for procurement under PEPFAR. Applicants should refer to cited guidances in this section for additional details on FDA's current thinking.

### *1. Controls*

If the drug substance is poorly soluble or is a small percentage of the drug product weight, applicants should consider drug substance particle size control, according to the recommendations described in the guidance for industry *Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances* (December 2000). If the drug substance can exist in different solid-state polymorphic forms, additional controls may be appropriate.

### *2. Impurities*

Batch analyses for at least three lots of drug substance produced by the same process that is to be used for the material used for the exhibit batch of drug product should be included in the DMF, NDA, or ANDA. If impurities exceed the recommended qualification thresholds on drug substance as described by the guidance for industry *Q3A(R2) Impurities in New Drug Substances* (June 2008), additional toxicological justification may be appropriate. If impurities are below the recommended Q3A(R2) qualification thresholds, there is no need for toxicological qualification unless the structure suggests unusual toxicology (e.g., there is a genotoxic substructure). If the residual solvents or elemental impurities in the drug substance exceed the recommendations in the guidances for industry *Q3C Impurities: Residual Solvents* (December 1997) and *Q3D(R2) Elemental Impurities* (September 2022), additional toxicological justification may be appropriate.

## D. Drug Product Issues

This section describes scientific issues regarding the drug product that may arise during FDA review of ARV drug product submissions intended to be eligible for procurement under PEPFAR. For more information on pharmaceutical development, applicants should refer to the guidance for industry *Q8(R2) Pharmaceutical Development* (November 2009).

*1. Controls and Impurities*

Drug products should be formulated using excipients that meet internationally recognized compendial standards. Information should be provided to support the safety of each excipient, particularly those derived from animals. Applicants should justify the use of novel excipients, using animal toxicity data if necessary.[47]

Identification of an impurity is not needed if the guidance for industry *Q3B(R2) Impurities in New Drug Products* (August 2006) identification threshold recommendation is not exceeded. For an FC ARV drug product, in general, the amount of an unknown peak should be calculated as a percentage of the smallest active peak.

*2. Water Content*

Given the likely exposure to high humidity in countries supported by PEPFAR, applicants should provide a water content specification, or a justification for not providing such a specification, for solid oral dosage forms.

*3. Markings and Labeling*

There are now a significant number of tentatively approved or approved drug products eligible for procurement under PEPFAR and prequalified by WHO, and FDA expects drug products to be marked and labeled so that they can be identified by medical professionals. Each dosage unit should be marked so that it can be readily identified, and different drugs from the same manufacturer should have distinct labeling.

*4. Scored Tablets*

If tablets are scored, testing should be performed to show that split tablets are suitable for their intended purpose. More information can be found in the guidance for industry *Tablet Scoring: Nomenclature, Labeling, and Data for Evaluation* (March 2013) (Tablet Scoring guidance). An applicant submitting a change amendment[48] to a tentatively approved application should also refer to the Tablet Scoring guidance.

Some RLD tablets are scored but would not be considered functionally scored tablets as described in the Tablet Scoring guidance. In these situations, versions of these ARV tablets eligible for procurement under PEPFAR should also be manufactured with a score. However, to support labeling claims for splitting these ARV tablets, the tablets should contain appropriate information for functional scoring. The Tablet Scoring guidance recommends a 90-day stability study for split tablets stored in pharmacy dispensing containers (no seal/no desiccant) for a period of 90 days at 25ºC/60 percent relative humidity (RH). However, for ARV drugs products

[47] See the guidance for industry *Nonclinical Studies for the Safety Evaluation of Pharmaceutical Excipients* (May 2005).

[48] See 21 CFR 314.60(b). See also section III.B.1., Amendments: Before Final Marketing Approval Request, and 21 CFR 314.70(b).

intended for use under PEPFAR, such testing should instead occur at 30°C/75 percent RH because of the conditions that may be encountered in climatic zones III and IV.[49]

### *5. Tablets Intended for Dispersion in Water or Other Liquids*

If the labeling indicates that the tablet may be dispersed in water or other liquids, appropriate testing should demonstrate that dispersion is feasible for this specific drug product. The following information should be included in the application:

- Information on how quickly the tablet breaks up in water or other liquids (e.g., typically, 2 teaspoons (10 milliliters) per tablet)

- Appropriate controls on process parameters, in-process tests, or specifications to ensure that the tablet will break up in water in a reasonably quick fashion

- Short-term stability data to show that the active ingredient is chemically stable when dispersed in water or the other liquids (e.g., to support a statement to drink the mixture within a certain time frame)

### *6. Packaging*

In most cases, FDA recommends child-resistant packaging although such a decision should be made after consultation with procuring organizations (e.g., U.S. Agency for International Development, U.S. Department of State's Office of Global AIDS Coordinator and Health Diplomacy) keeping in mind the local laws of the country where the drug product is to be used.

Some applicants have expressed a preference for demonstrating the stability of their drug products in non-child-resistant packaging, such as in bottles and blisters that applicants believe are acceptable to the regulatory authorities of the PEPFAR-supported recipient countries. FDA believes that issues related to special packaging (e.g., child-resistant, senior-friendly) are best approached in the context of the PEPFAR-supported recipient country's regulations and prescribing practices; accordingly, it may be appropriate to grant a tentative approval with this type of packaging. However, when patents and/or exclusivities expire for the referenced drug products, applications for final marketing approval in the United States must comply with all final approval requirements, including relevant U.S. packaging and labeling regulations.[50]

Applicants should refer to the guidances for industry *Container Closure Systems for Packaging Human Drugs and Biologics* (May 1999) and *Container Closure Systems for Packaging Human Drugs and Biologics — Questions and Answers* (May 2002) for recommendations on the information needed for the container closure systems.[51] FDA anticipates that procurement

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[49] See the International Council for Harmonisation (ICH) guidance for industry *Q1A(R2) Stability Testing of New Drug Substance and Products* (November 2003).

[50] See footnote 30.

[51] See also MAPP 5015.5 Rev. 1 *CMC Reviews of Type III DMFs for Packaging Materials*.

organizations, applicants, and regulatory authorities will cooperate to share information on the equivalence of container closure system protection.

The shelf-life specification should be the same for all packaging configurations. Different packaging configurations may have different expiration dating periods to ensure that the drug product meets the specification throughout its shelf life. It is acceptable to have a tighter internal release specification, but the regulatory specification applies throughout the approved expiration dating period to all packaging configurations.

### *7. Stability*[52]

As provided in 21 CFR 314.50(d)(1)(ii)(*a*), applicants must demonstrate the stability of the drug product. Generally, this includes accelerated and long-term stability data; the application should include stability data obtained from the drug product in the commercial packaging.

### *8. Stability Storage Conditions*

Drug products distributed under PEPFAR are likely to be used in several countries with hot and dry or hot and humid conditions (climatic zones III and IV).[53] Given the conditions that may be encountered during distribution and storage under programs such as PEPFAR, applicants should generate data on the stability of their drug products under the conditions specified by regulatory authorities in the recipient countries and WHO.

At present, long-term studies at 30°C/75 percent RH and 6-month accelerated studies at 40°C/75 percent RH will cover use and registration in all climatic zones. If the data obtained at 30°C/75 percent RH are satisfactory, data obtained at 25°C/60 percent RH are not generally needed.

FDA recommends in-use stability studies for ARV drug products containing amorphous dispersions (e.g., products containing ritonavir) and/or tenofovir prodrugs (e.g., products containing tenofovir disoproxil fumarate (TDF) or tenofovir alafenamide (TAF)). These ARV drug products have a sensitivity to moisture, and studies could support bottles that are intended to be dispensed to patients and then opened daily for 90 days or 180 days. By combining results from long-term and in-use stability studies at 30°C/75 percent RH, applicants can predict the amount of a particular degradant by summing the following values:

- The amount of degradant present in freshly manufactured drug product

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[52] For more information, see the guidances for industry *ANDAs: Stability Testing of Drug Substances and Products* (June 2013) and *ANDAs: Stability Testing of Drug Substances and Products, Questions and Answers* (May 2014) and the ICH guidances for industry *Q1A(R2) Stability Testing of New Drug Substance and Products* and *Q1C Stability Testing for New Dosage Forms* (November 1996).

[53] Deitz, R, K Feilner, F Gerst, and W Grimm, 1993, Drug Stability Testing — Classification of Countries According to Climatic Zone, Drugs Made in Ger, 36:99–103.

- The amount of degradant likely to be formed as the sealed bottle sits in storage (rate of degradation (percent degradation per month) times expiration dating period (in months))

- The amount of degradant that is formed during the in-use study

The amount of degradation (or reduction in assay) predicted at the end of expiration can be compared to the acceptance criteria for stability. Depending on the outcome of these studies, it may be appropriate to tighten the release acceptance criteria for major degradants (or assay) to ensure that the acceptance criteria for stability are met. If desiccant is included in the bottle and retained during the in-use study, FDA in general would recommend a labeling statement such as, *"Store and dispense in original bottle, protect from moisture, and keep bottle tightly closed. Do not remove desiccant."* for NDAs for ARV drug products eligible for procurement under PEPFAR.

FDA recommends a storage labeling statement such as *"Store below 30°C (86°F)"* for NDAs for ARV drug products eligible for procurement under PEPFAR if supported by data obtained at 30°C/75 percent RH. In general, ANDAs for ARV drug products eligible for procurement under PEPFAR will follow storage recommendations for the RLD.

These recommendations apply to the drug product. Because the drug substance is generally held at more controlled conditions (e.g., at the manufacturing site) it is typically tested under less stressful conditions (e.g., 25°C/60 percent RH).

*9. Amount of Stability Data*

Currently, FDA recommends that at least 6 months of stability data obtained under long-term (e.g., 30°C/75 percent RH) and accelerated (e.g., 40°C/75 percent RH) conditions be submitted with the initial application. These data should be obtained for at least three batches of drug product manufactured by a process representative of the intended commercial process.[54] At least two of these batches should be a minimum of 10 percent of the intended commercial scale, unless otherwise justified. When appropriate, the design of stability studies can incorporate bracketing and matrixing.[55] Additional stability data may be requested by FDA during the review cycle. If a 24-month expiration date is desired, 12 months of stability data should be submitted by the middle of the review cycle.

*10. Assessment of Stability Data*

Assessment of stability should include assaying each active ingredient to meet acceptance criteria of 90 to 110 percent of labeled strength, determining individual and total impurity levels,

[54] See the guidances for industry *ANDAs: Stability Testing of Drug Substances and Products* and *ANDAs: Stability Testing of Drug Substances and Products, Questions and Answers* and the ICH guidances for industry *Q1A(R2) Stability Testing of New Drug Substance and Products* and *Q1C Stability Testing for New Dosage Forms*.

[55] See the ICH guidance for industry *Q1D Bracketing and Matrixing Designs for Stability Testing of New Drug Substance and Products* (January 2003).

and measuring dissolution rates. Applicants should submit data on moisture uptake in the dosage form, which is important if the drug product is to be packaged in polymer/foil blisters that are not as impervious to moisture as high-density polyethylene bottles or foil/foil blisters.

#### *11. Expiration Dating Period*

Applicants should provide justification of the proposed expiration dating period based on actual stability data for the drug product in the application, supportive stability data for pilot batches or similar drug products, qualitative or statistical analysis of trends, etc. Applicants should include sufficient time points on the stability protocol to cover any anticipated future extension of expiration. To facilitate the effective delivery of drug products distributed outside of the U.S. under PEPFAR, FDA encourages applicants to extend the expiration dating period to 36 or 48 months, once sufficient supporting stability data have been acquired. An applicant could acknowledge its commitment to submit amendments after tentative approval for extension of expiration in a timely manner by including a statement in the original application (section 3.2.P.8.2, Postapproval Stability Protocol and Stability Commitment, of the common technical document is recommended). Once sufficient stability data have been obtained (typically 24 or 36 months of data), FDA encourages applicants to submit an amendment after tentative approval to extend the expiration. Applicants should include the wording "Priority Review Requested" in the submission and the cover letter and should not include other changes in the expiration-extension amendment. See section VI. E., CMC Changes After a Tentative Approval, for recommended approaches to extending the expiration dating period.

### E. CMC Changes After a Tentative Approval

This section addresses some of the common CMC changes after tentative approval of ARV drug products eligible for procurement under PEPFAR.

#### *1. Addition of a New Drug Substance Manufacturer or Manufacturing Site, Drug Product Manufacturer, or Manufacturing Site or Testing Site*

A new manufacturer (supplier) of the drug substance should be submitted as a major change amendment. A new manufacturing site for an existing manufacturer that has not been previously inspected by FDA should also be submitted as a major change amendment. In contrast, a new manufacturing site for an existing manufacturer that has been previously inspected by FDA should be submitted as a moderate change amendment. An inspection may take place, even if previously inspected, depending on review of the submission. Note that the manufacturing process needs to be validated at the new manufacturing site, regardless of previous manufacturing experience at other sites. A Letter of Authorization to allow an applicant to reference the DMF should be submitted to the DMF, with copies submitted to the relevant application(s).

#### *2. Extension of Expiration Dating Period*

Depending on the data available to justify the extension, the two following approaches are examples of what may be appropriate:

a. Submitting a major change amendment proposing to extend the expiration dating period for the drug product on the basis of real-time data plus extrapolation using acceptable statistical methods,[56] for example, extrapolating to a 36-month expiration dating period based on statistical analysis of 24-month stability data on the original three registration batches.

b. Proposing extension of the expiration dating period through a minor change amendment based on real-time stability data from pilot-scale or larger/commercial-scale batches following the acceptable stability protocol for an application that has already received a tentative approval action, for example, proposing a 36-month expiration dating period based on 36-month stability data on the original three registration batches.

*3. Changes in Excipient Specifications*

Applicants should submit a change made to comply with U.S. Pharmacopeia/National Formulary (USP/NF) that adds a new test or tightens existing acceptance criteria in an excipient specification in a minor change amendment. Applicants should submit deletions of tests or relaxation of limits as a moderate change amendment if the relaxation or deletion is in compliance with an updated USP/NF monograph. Applicants should submit other deletion of tests or relaxations of limits as major change amendments.

*4. Changes to the Stability Testing Program*

Applicants should submit any changes to the stability testing protocol after tentative approval as major change amendments, except the addition of time points or deletion of time points beyond the approved expiration dating period, which may be submitted as a minor change amendment.

## VII. LABELING AND PRESCRIBING INFORMATION

ARV drug products eligible for procurement under PEPFAR must comply with all applicable labeling requirements.[57] This section highlights certain labeling considerations specific to ARV drug products eligible for procurement under PEPFAR. For pediatric dosage forms, the proposed labeling for the drug product should provide clear instructions so that the patient's caregiver can administer the appropriate dose of the drug product.[58] In some cases, it may be appropriate for written and pictorial Instructions for Use intended for caregivers to be included in the prescribing information.[59]

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[56] See the ICH guidance for industry *Q1E Evaluation of Stability Data* (June 2004).

[57] See generally section 502 of the FD&C Act; 21 CFR part 201, Labeling.

[58] See, for example, 21 CFR 201.57(c)(9)(iv) and 201.80(f)(9).

[59] See the guidance for industry *Instructions for Use — Patient Labeling for Human Prescription Drug and Biological Products — Content and Format* (July 2022).

The inclusion of product-identifying information (e.g., National Drug Code (NDC) numbers), if relevant, on the labeling (e.g., container labels, carton labeling, prescribing information) of tentatively approved drug products eligible for procurement under PEPFAR can assist with drug product differentiation. .

For tentatively approved 505(b)(2) NDA drug products eligible for procurement under PEPFAR, it is not necessary to revise the product labeling whenever there are minor updates in the labeling for the listed drug(s) (on which the 505(b)(2) NDA relied upon for safety and efficacy). Applicants must submit updated labeling amendments for the drug products if the following scenarios apply (21 CFR 201.57(a)(5)):

- When submitting a chemistry change amendment that affects the labeling

- There is a significant update in the labeling for the listed drug(s) on which the 505(b)(2) NDA relied upon for safety and efficacy (e.g., new information for Limitations of Use, the BOXED WARNING section, the DOSAGE FORMS AND STRENGTHS section, the CONTRAINDICATIONS section, or the WARNINGS AND PRECAUTIONS section that is applicable to the ARV drug product eligible for procurement under PEPFAR).

For tentatively approved 505(j) ANDA drug products eligible for procurement under PEPFAR, labeling must be the same as the last approved labeling for the RLD, except for differences as provided for in section 505(j)(2)(v) of the FD&C Act and 21 CFR 314.94(a)(8)(iv) .

## VIII. OTHER REGULATORY CONSIDERATIONS

This section briefly discusses other considerations for ARV drug products intended to be eligible for procurement under PEPFAR.

### A. User Fees

#### *1. NDAs*

By law, FDA must assess a user fee on human drug applications and an annual prescription drug program fee, subject to certain exceptions.[60] However, the law provides that under certain circumstances FDA can grant a waiver or reduction in fees.[61] Potential waivers for ARV drug products eligible for procurement under PEPFAR (for NDAs but not ANDAs) are addressed in the draft guidance for industry *PDUFA Waivers, Reductions, and Refunds for Fixed-Combinations and Single-Entity Versions of Previously Approved Antiretrovirals under*

[60] Section 736(a) of the FD&C Act; 21 U.S.C. 379h(a). The application fee is the most significant of the fees. Application reviews do not begin until user fees are paid.

[61] Section 735(d) of the FD&C Act.

*PEPFAR*.[62] Drug products that are included in the list of needed ARV drug products[63] on the FDA's PEPFAR database[64] may be considered for potential NDA user fee waivers as appropriate.

*2. ANDAs*

For ANDAs, application and facility fees are assessed according to the Generic Drugs User Fee Act (GDUFA). Applicants should refer to information found on the FDA's Generic Drug User Fee Amendments web page available at https://www.fda.gov/industry/fda-user-fee-programs/generic-drug-user-fee-amendments for additional information on fee structure and amounts.

### B. Pediatric Requirements

The Pediatric Research Equity Act (PREA)[65] requires that any NDA[66] or BLA, or supplement to such application, for a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration contain pediatric assessments, unless the requirement is waived, deferred, or inapplicable. Such assessments "shall contain data, gathered using appropriate formulations for each age group for which the assessment is required, that are adequate (i) to assess the safety and effectiveness of the drug . . . for the claimed indications in all relevant pediatric subpopulations; and (ii) to support dosing and administration for each pediatric subpopulation for which the drug . . . is safe and effective."[67] Pediatric studies may be deferred if (1) the drug product is ready for approval for use in adults before pediatric studies are complete, (2) additional safety or effectiveness data need to be collected, or (3) there is another appropriate reason for the deferral; and if the applicant submits required information[68] to support the deferral.[69] Pediatric studies will be waived if (1) the studies are impossible or highly

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

[63] The separate list of ARV drug products, Antiretroviral Drug Products Needed for Use Under PEPFAR, can be found under question 6, What PEPFAR products can companies submit for FDA review?, at FDA's PEPFAR Database on the Frequently Asked Questions web page available at https://www.fda.gov/international-programs/presidents-emergency-plan-aids-relief-pepfar/pepfar-database-frequently-asked-questions. This list is revised periodically to address current public health needs.

[64] The FDA's PEPFAR database is available at https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=pepfar.page.

[65] Public Law 108-155 (2003), codified at section 505B of the FD&C Act (21 U.S.C. 355c). Although section 505B has been amended since the passage of PREA, by convention, that section is often referred to as PREA, and we adopt that convention in this guidance.

[66] PREA does not apply to drug products submitted in an ANDA under section 505(j) of the FD&C Act.

[67] 21 U.S.C. 355c(a)(2)(A).

[68] Described in 21 U.S.C. 355c(a)(4)(A)(ii).

[69] See 21 U.S.C. 355c(a)(4)(A). See also 21 U.S.C. 355c(a)(4)(C) and (D).

impracticable, (2) there is evidence strongly suggesting that the drug product would be ineffective or unsafe in all pediatric age groups, or (3) the drug product does not represent a meaningful therapeutic benefit over existing therapies and is not likely to be used in a substantial number of pediatric patients.[70] In certain cases, as appropriate, FDA will grant a partial waiver with respect to a specific pediatric age group(s).[71]

PREA, as described above, applies to NDAs for ARV drug products eligible for procurement under PEPFAR. Generally, most ARV drug products indicated for pediatric populations are labeled by weight-band dosing, and DAV recommends designing the PREA assessments accordingly. For some SE or FC ARV drug products submitted under section 505(b)(2) of the FD&C Act, available information for the reference drug product may provide sufficient information to support pediatric use for at least some part of the pediatric population. For ARV drug products not intended for use in specific pediatric age (or weight) groups, FDA encourages applicants to contact DAV about the possibility of a waiver or deferral.

Submission of NDAs for ARV drug products discussed in this guidance are usually not preceded by end-of-phase 2 meetings or pre-NDA meetings. Sometimes, sponsors seek pre-investigational new drug application (pre-IND) advice regarding design of relative bioavailability studies. Sponsors seeking pre-IND advice should consider providing an initial pediatric study plan (iPSP) at that time.[72] A sponsor that has not met with FDA or sought advice before submission of an application should provide an iPSP, submitted to a pre-IND, to DAV when the sponsor submits a request for a user fee waiver.

### C. Adverse Event Reporting

For approved ANDAs or NDAs, applicants must comply with adverse event reporting requirements (i.e., reports of serious and unexpected adverse events within 15 days of receipt of the information by the applicant or its affiliates).[73] For tentatively approved ARV drug products to be distributed in PEPFAR-partner countries, a system of collecting and reporting adverse drug events by the distributor is encouraged (e.g., through governmental or nongovernmental agencies distributing the drug products).

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[70] See 21 U.S.C. 355c(a)(5)(A). See also 21 U.S.C. 355c(a)(4)(C) and (D).

[71] See 21 U.S.C. 355c(a)(5)(B).

[72] For more information on iPSPs, see the guidance for industry *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Initial Pediatric Study Plans* (July 2020).

[73] 21 CFR 314.80 and 314.81.