Information for Industry on FDA's Tentative Approval Process Under the PEPFAR Program

Q1. What is a Tentative Approval?

A1. A tentative approval is a notification issued by the Food and Drug Administration (FDA) to drugs that otherwise meet the statutory and regulatory requirements for approval but cannot be approved for marketing in the United States because of patents or exclusivities related to the reference listed drug (RLD) (e.g., brand-name drug) upon which they rely. The U.S. President's Emergency Plan for AIDS Relief (PEPFAR) program utilizes drugs that the FDA has tentatively approved to ensure that safe, effective, quality-assured antiretrovirals (ARV), the medicines used to treat and prevent HIV, are available for purchase and distribution under PEPFAR.

Many tentatively approved ARV are generic drugs, which are duplicates, except for differences permitted by FDA regulations, of previously FDA-approved drugs. Some tentatively approved ARV are new versions of previously approved ARV, such as new triple fixed combinations as complete regimens, new strengths, or innovative formulations that are specifically designed for children not able to swallow conventional tablets or capsules.

An application seeking tentative approval is reviewed by the FDA using the same criteria for safety, efficacy, and quality as any other FDA-approved drug. Tentatively approved drugs, however, cannot be marketed and sold in the United States because their approval is delayed until the FDA issues an approval letter after all patent and exclusivity issues have been resolved and after any necessary additional review of the application. Tentatively approved ARV, however, can still be purchased for use in high prevalence, resource-constrained countries that partner with PEPFAR, the Global Fund or other similar international programs.

Q2. What are the regulatory pathways for review of PEPFAR ARV?

A2. The Federal Food, Drug, and Cosmetic Act (the Act) is a federal law enacted by U.S. Congress and establishes the legal framework within which the FDA operates. There are three types of new drug applications described in section 505 of the Act. Their respective regulatory pathways are summarized as follows:

a. 505(b)(1) new drug application (NDA): also known as a stand-alone application that contains, among other things, full reports of investigations of safety and effectiveness that were conducted by or for the applicant or for which the applicant has a right of reference or use. This type of NDA is typically only eligible for approval. One example is Truvada (emtricitabine and tenofovir disoproxil fumarate).
b. 505(b)(2) NDA: an application that contains, among other things, 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. This type of NDA is eligible for approval or tentative approval. One example is, tenofovir disoproxil fumarate, lamivudine, and dolutegravir (TLD).
c. 505(j) abbreviated new drug application (ANDA): 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. An ANDA is eligible for approval or tentative approval. One example is emtricitabine and tenofovir disoproxil fumarate, as a generic version of Truvada.

The FDA's tentative approval process is an existing practice utilized by the PEPFAR program. Because ARV submitted as 505(b)(1) NDAs are usually eligible for approval rather than tentative approval, these

applications are not discussed further in this document. Rather, the information presented here focuses on the tentative approval of ARVs for HIV-1 treatment or prevention submitted in a 505(b)(2) NDA or an ANDA.

The FDA will not issue a tentative approval in lieu of marketing approval when there are no patent and exclusivity barriers to approval.

Q3. When can an application for tentative approval be submitted under PEPFAR?
A3. Companies seeking tentative approval of ARV under the PEPFAR program submit either a 505(b)(2) NDA to the FDA's Division of Antivirals of the Office of New Drugs or an ANDA to the FDA's Office of Generic Drugs. Companies that are interested in submitting applications for use under PEPFAR but reside outside the United States are required to have an authorized U.S. agent who resides or maintains a place of business within the United States.

In the PEPFAR context, companies who are seeking tentative approval of ARV in a 505(b)(2) NDA or an ANDA generally submit a Paragraph III [21 CFR 314.94(a)(12)(i)(A)(3)] certification to patents listed in the FDA's *Approved Drug Products with Therapeutic Equivalence Evaluations* (also known as the Orange Book) at the time of submission of the application.

If the RLD (e.g., brand-name drug) upon which the ARV relies has 5-year new chemical entity (NCE) exclusivity, the company cannot submit to the FDA and the FDA cannot accept for review any 505(b)(2) NDA or ANDA for a drug product that contains the same *active moiety as the new chemical entity* until the 5-year NCE exclusivity period expires. However, the brand-name company may selectively waive its NCE exclusivity; thus, if a company secures a selective waiver from the brand-name company, this would allow that company to submit (and the FDA to receive and review) a 505(b)(2) NDA or an ANDA that is seeking tentative approval for use under PEPFAR.

Q4. What are the timelines for review of tentative approval applications for PEPFAR?
A4. The FDA establishes timelines for review of drug applications based on the type of application (i.e., NDAs and ANDAs).

The FDA created a two-tiered review designation system for all original NDAs - *Standard Review* and *Priority Review.* A *Priority Review* designation means the FDA's goal is to take action on an application within six months (compared to 10 months under *Standard Review*). For 505(b)(2) NDAs submitted for use under PEPFAR, the FDA decides on the review designation for every application and will consider a *Priority Review* designation for the first three applications of a particular kind (e.g., new fixed-combination or formulations specific to children) that are currently listed as a priority in the PEPFAR ARV Prioritization List or the *Antiretroviral Drug Products Needed for Use Under PEPFAR* list. After that, subsequent applications will be designated a *Standard Review.*

Currently, original ANDAs submitted for use under PEPFAR are eligible for priority review and may receive either a shorter goal date or an expedited review as outlined in CDER's Office of Generic Drugs MAPP 5240.3 Rev.6 with performance goals set by the Generic Drug User Fee Amendment (GDUFA) through September 2027 (GDUFA III) Commitment Letter. For an original ANDA to qualify for prioritization, the submission may not contain a paragraph IV certification.

Q5. What are the application fees for PEPFAR applications?

A5. Federal law authorizes the FDA to collect fees (called user fees) from companies that submit drug applications for review. User fees help fund certain the FDA inspections and other programs. The two relevant user fee programs are the Prescription Drug User Fee Act (PDUFA) and the NDA and GDUFA. ANDA fees are determined under PDUFA and GDUFA, respectively.

All 505(b)(2) NDAs submitted under PEPFAR require application fees. However, the FDA may waive the application fee for ARV applications meeting the statutory criteria for a barrier-to-innovation waiver under section 736(d)(1)(B) of the Act. When finalized, the FDA's draft PEPFAR Waivers Guidance will reflect the FDA's current thinking on this topic. ANDAs submitted under PEPFAR do not qualify for a fee waiver and companies must pay the relevant fees according to GDUFA III.

Additional resources on PEPFAR Applications:

a. PEPFAR Lead Guidance, August 2023: *Fixed-Combinations and Single-Entity Versions of Previously Approved Antiretrovirals for the Treatment or Prevention of HIV-1 Under PEPFAR*

b. Pre-submission guidance for NDAs: Division of Antivirals' Pre-IND Consultation Program

c. ARV drug products for 505(b)(2) NDAs list: *Antiretroviral Drug Products Needed for Use Under PEPFAR*.

d. The FDA's PEPFAR Database Frequently Asked Questions. This list is revised periodically to address current public health needs.