
Guidance for Industry

Fixed Dose Combinations, Co-Packaged Drug Products, and Single-Entity Versions of Previously Approved Antiretrovirals for the Treatment of HIV

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

**Procedural
October 2006**

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This represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

This guidance is intended to encourage sponsors to submit applications to the Food and Drug Administration (FDA) for approval of fixed dose combination (FDC) and co-packaged versions of previously approved antiretroviral therapies for the treatment of human immunodeficiency virus (HIV).² The guidance seeks to clarify what regulatory requirements apply to such applications, what issues might be of concern, and how these issues should be addressed. Different considerations apply depending on whether (1) a sponsor owns or has a right of reference to all of the data required to support an application or (2) whether a sponsor plans to rely on literature or FDA's findings of safety and effectiveness for an approved drug. This guidance addresses the issues associated with these different scenarios. Although this guidance focuses on FDC and co-packaged products, the principles outlined in this guidance also apply to single-ingredient copies of antiretroviral drugs that are components of the regimens listed in Appendix B. On a case-by-case basis, these single-ingredient copies may be reviewed in an expedited time frame. The guidance provides scientific and technical details on the submission of new drug applications (NDAs) and abbreviated new drug applications (ANDAs) for both single and combination products.

¹ This guidance has been prepared by the Division of Antiviral Drug Products in the Center for Drug Evaluation and Research (CDER) in cooperation with the Office of Regulatory Policy, CDER.

² For the purposes of this guidance, a *co-packaged product* consists of two or more separate drug products in their final dosage form, packaged together with appropriate labeling to support the combination use. A *fixed dose combination* product is one in which two or more separate drug ingredients are combined in a single dosage form.

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This guidance is not an exhaustive document on the development and approval of antiretroviral combinations. FDA is able to provide more complete, detailed advice in the context of specific drug development programs. Therefore, FDA strongly recommends that any company interested in pursuing the approval of FDC or co-packaged products consult with FDA as early as possible to ensure that applications are complete. FDA also recommends that sponsors submit available information regarding their products in advance of an official application to enhance the efficiency of the review process.

For additional guidance, three attachments are included. Attachment A outlines some regulatory scenarios for approval of FDC or co-packaged products for the treatment of HIV. Attachment B lists examples of drug combinations that are supported by current clinical data and considered acceptable for FDC/co-packaging. Attachment B also contains label and literature references supporting the safety and efficacy of specific two- and three-drug antiretroviral combinations. Attachment C lists drug combinations not considered acceptable for FDC/co-packaging.

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

II. BACKGROUND

Combination antiretroviral therapy is essential for the treatment of HIV/AIDS. The goals of HIV therapy are to maximally and durably suppress the virus to allow recovery of the immune system and reduce the emergence of HIV resistance. At least three active drugs, usually from two different classes, are required to achieve the above mentioned therapeutic goals. In the United States and developing countries, simplified HIV regimens in the form of FDC or co-packaged drugs (such as blister packs) may facilitate distribution and improve patient adherence.

For treatment-naïve patients (meaning those who are first initiating antiretroviral therapy) several preferred regimens are listed in the Department of Health and Human Services (HHS) treatment guidelines and the International AIDS Society guidelines.³ For treatment-experienced patients, the choice of combination regimens is more complex and individualized. Therefore, three-drug FDC or co-packaged products are probably most

³ See Department of Health and Human Services (HHS) Panel on Clinical Practice for the Treatment of HIV Infection, Guidelines for the Use of Antiretroviral Agents in HIV-1 Infected Adults and Adolescents, <http://www.aidsinfo.nih.gov/>; Yeni PG, SM Hammer, MS Hirsch, et al., "Treatment for Adult HIV Infection: 2004 Recommendations of the International AIDS Society-USA Panel," *JAMA*, 2004 Jul 14; 292(2):251-65.

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useful for treatment-naive patients; however, this may change as treatment guidelines for treatment-experienced patients evolve.

Although more than 20 unique antiretroviral drugs are approved in the United States under section 505 of the Federal Food, Drug, and Cosmetic Act (the Act) (21 U.S.C. section 355), only a few are approved for use as FDC products. Some antiretrovirals should not be combined because of overlapping toxicities and potential viral antagonism. Other antivirals should not be used in pregnant women and other special populations.

FDC formulations that have not been evaluated by the FDA are being promoted for use in resource poor nations where HIV-1 has reached epidemic proportions.⁴ These FDCs may offer cost advantages and allow simplified dosing because two or three drugs are combined in one pill. However, FDA has not evaluated the safety, efficacy, or quality of many of these products. Antiretroviral drugs whose safety, efficacy, and quality do not conform to expected regulatory standards may pose a threat to individual patients by increasing the chances of substandard performance, which may lead to treatment failure and to the emergence and spread of resistant virus.

FDA believes that when adequate evidence of safety and efficacy exists for the use of combination therapy with individually approved HIV drugs, the path to regulatory approval of an FDC or co-packaged configuration of those drugs is straightforward. FDA is prepared to move swiftly to evaluate such products when applications are submitted for approval.

III. HIV THERAPY AND RESOURCE POOR SETTINGS

In the State of the Union address on January 28, 2003, President Bush announced the President's Emergency Plan for AIDS Relief (PEPFAR). PEPFAR provides \$15 billion over 5 years with the goal of preventing 7 million new infections, treating 2 million HIV infected people, and caring for 10 million HIV infected individuals and AIDS orphans. Drug treatment plays a major role in this relief plan, and it is important that resources are spent on treatments that have been demonstrated to be safe and effective. Of note, only antiretroviral drugs that undergo a stringent review by a regulatory authority such as FDA are eligible for procurement under PEPFAR. As a result, this guidance encourages the development of antiretroviral drug products to promote wider availability of therapy for HIV/AIDS.

⁴ Although there are two types of HIV virus (HIV-1 and HIV-2), most of the AIDS pandemic is due to infection with HIV-1. HIV-2 is less prevalent, particularly outside of West Africa; HIV-2 also appears to be less pathogenic and less efficiently transmitted compared to HIV-1. Clinical studies of antiretroviral drugs for the treatment of HIV infected patients have thus far focused primarily on the treatment of the HIV-1 virus. In fact, some of the drugs and drug combinations referred to in this guidance are clearly not effective (i.e., lack activity against HIV-2 in in vitro studies) or have not been shown to be effective in the treatment of HIV/AIDS caused by HIV-2. This guidance addresses FDC or co-packaged products to treat patients with HIV/AIDS caused by the HIV-1 virus.

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IV. GENERAL CONSIDERATIONS

A. To Which Products Does this Guidance Apply?

This guidance is primarily aimed at combination antiretroviral drug products for which the individual drug components of the combination are already FDA approved and for which substantial evidence of safety and efficacy of the specific combination already exists. FDA encourages potential applicants to contact the Division of Antiviral Products with regard to combinations for which safety and effectiveness are not yet supported by currently available clinical data.

Although this guidance focuses on FDC and co-packaged products, the scientific principles outlined in this guidance also apply to single ingredient copies of antiretroviral drugs that are components of regimens listed in Appendix B. Differences in regulatory processes for NDAs and ANDAs are described in the relevant sections of the guidance.

B. What Regulatory Procedures Apply to FDC and Co-Packaged HIV Products?

Priority review and fast track designations are already available and are applicable to these products.

- A priority review designation provides for the review of an application in 6 months or less.⁵ We expect, however, that the applications described in this guidance could be reviewed within shorter time frames.
- Fast track designation offers a number of advantages that can facilitate drug development and approval (see the guidance for industry on *Fast Track Drug Development Programs — Designation, Development, and Application Review*). Fast track designation encompasses programs that were already in existence before the creation of the fast track program, such as subpart E — Drugs Intended to Treat Life-threatening and Severely-Debilitating Illnesses (21 CFR 312.80 through 312.88), priority review, and accelerated approval (21 CFR 314.500). In addition, a fast track designation allows parts of a marketing application to be accepted before submission of the complete application (i.e., *rolling* submission).

To facilitate rapid development and approval of combination HIV therapies, FDA is prepared to meet with applicants early in the development stages of either a co-packaged or FDC product to discuss the appropriateness of the combination, the dosing strength, and the appropriate nonclinical and chemistry, manufacturing, and controls (CMC) data.

⁵ FDA procedures have been established for these designations (e.g., CDER MAPP 6020.3, *Priority Review Policy*).

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For products developed by applicants who own or have a right of reference to all the underlying preclinical, safety, and efficacy data required to support approval, the regulations on 505(b)(1) applications apply. Regulations that govern 505(j) or 505(b)(2) applications, as summarized below, apply to products developed by applicants who do not own or have a right of reference to all the underlying preclinical, safety, and efficacy data required to support approval.

An ANDA filed under section 505(j) of the Act (commonly referred to as a *generic* drug application) is an application that contains information to show that the proposed product has, among other things, the same active ingredient, dosage form, strength, route of administration, labeling, quality, performance characteristics, and conditions of use as a previously approved product (i.e., the reference listed drug (RLD)) and that the drug is bioequivalent to the RLD. A reference listed drug is defined as a drug product that has previously been approved in the United States and is listed in FDA's *Approved Drug Products With Therapeutic Equivalence Evaluations* (commonly known as the Orange Book). An ANDA can be submitted only if the RLD on which it relies for approval has previously been approved in the United States and is listed in the Orange Book. Generally, the following types of applications for antiretroviral agents can be submitted as ANDAs:

- Applications for duplicates of single FDA-approved antiretroviral drugs
- Applications for duplicates of currently FDA-approved FDCs
- Applications for duplicates of subsequently FDA-approved innovator FDC

Applications for not previously approved single antiretroviral drug products must be submitted as 505(b)(1) NDAs. Applications for FDCs, or co-packaged products for which no RLD exists must be submitted as either 505(b)(1) or 505(b)(2) NDAs. FDA believes that adequate clinical studies confirming the safety and efficacy of the FDC or co-packaged products listed in Attachment B have already been conducted; therefore, new clinical studies are not needed to support applications for the listed products. For combinations listed in Attachment B, and for which the applicant does not have a right of reference to data establishing the safety and efficacy of the combination, FDA anticipates that applicants will be able to submit a 505(b)(2) application. Please refer to Attachment A for scenarios for approval of FDC/co-packaged combinations.

A *tentative approval* may be granted for FDC or co-packaged products that cannot be marketed in the United States because of existing patents and/or exclusivity. Products that receive a tentative approval undergo the same FDA review as products that are approved and marketed in the United States, and should meet the same safety, efficacy, and quality standards, including manufacturing and bioequivalence (BE) study inspections. When significant changes are made after a tentative approval action (e.g., addition of new manufacturing facilities, important new safety information), appropriate data should be submitted in an amendment to the application. Approximately 180 days before marketing in the United States becomes possible (i.e., patent and exclusivity issues have been resolved) the applicant should submit a minor amendment requesting full approval. That amendment should include final printed labels and labeling complying

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with all U.S. regulations (e.g. uniqueness of drug product appearance in accordance with 21 CFR 206; child-resistant packaging in accordance with 16 CFR 1700). This amendment should also either describe all significant changes to the product and manufacturing processes made since tentative approval, or certify that no significant changes have been made.

C. What Are the Characteristics of Potential Regimens for FDC or Co-Packaged HIV Therapies?

FDC or co-packaged HIV products can simplify regimens to allow easier distribution and improved patient adherence, particularly in resource poor settings. Proposed combination products should be relatively well tolerated and easy to administer while providing potency and a sufficient barrier to the emergence of drug resistance. FDC or co-packaged products should have the following important characteristics:

- They contain two or more components of an established fully suppressive regimen.
- They require a once- or twice-daily administration.
- They can be recommended as a preferred or alternative regimen (or regimen component) in treatment guidelines.⁶
- They have clinical efficacy and safety data that support use of the combination.
- They can be commonly used in treatment-naive patients.
- They have drug interaction and toxicity profiles that allow for concomitant dosing.
- They contain components with compatible food and fluid requirements.

Sponsors should take into account the required dosing frequency of each of the components. The components of an FDC should have identical dosing frequency and similar food instructions. Co-packaged products may include products with different dosing frequencies (once or twice daily) if the packaging design clearly delineates the dosing schedules in a user-friendly format that facilitates adherence. Sponsors should consider differences in food instructions between individual components when developing co-packaged products.

Pharmaceutical sponsors and other investigators have already conducted a substantial number of clinical studies of triple-combination regimens, particularly in treatment-naive patients. Based on these studies, several treatment guidelines⁷ describe preferred and alternative HIV treatment regimens for initial therapy. Preferred triple-treatment regimens consist of two drugs from the nucleoside (or nucleotide) reverse transcriptase inhibitor (NRTI) class and one drug from either the non-nucleoside reverse transcriptase inhibitor (NNRTI) class or the protease inhibitor class.

Information from clinical trial data and other scientific data (e.g., in vitro studies of resistance) show that three active antiretroviral agents are usually required to adequately

⁶ See footnote 3.

⁷ See footnote 3.

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sustain virologic control of HIV over the long term. The contribution of each antiretroviral in the type of combination regimens mentioned above to the overall efficacy and potency of a regimen has also been established in clinical trials. In fact, all approved antiretroviral agents are specifically indicated and labeled for use in combination with other antiretroviral agents. The combined use of antiretroviral drugs reduces the emergence of resistance and prolongs the usefulness of these drugs.

To encourage development of FDC and co-packaged products, FDA created a list of regimens and regimen components (Attachment B) for which the clinical safety and efficacy of concomitant use have been evaluated and described in product labeling or peer reviewed literature. FDA expects that FDC or co-packaged products for combinations on this list could be developed without conducting new clinical efficacy and safety studies, and that FDCs consisting of combinations on the attached list satisfy the principles outlined in 21 CFR 300.50 with regard to safe and effective use in combination.⁸

Inclusion criteria for this list of regimens and regimen components are:

- Approved individual components
- Two-drug nucleoside analogue components⁹ (to be used with a protease inhibitor or NNRTI)
- Three-drug regimens, consisting of two NRTIs and a protease inhibitor or NNRTI
- Once- or twice-daily dosing
- Triple regimen (or two-drug component) studied for at least 48 weeks in trials evaluating changes in HIV-RNA and CD₄ cells¹⁰

⁸ Regulations at 21 CFR 300.50 describe FDA's policy for the approval of fixed combination prescription drugs for humans. The rule states in pertinent part, "Two or more drugs may be combined in a single dosage form when each component makes a contribution to the claimed effects and the dosage of each component (amount, frequency, duration) is such that the combination is safe and effective for a significant patient population requiring such concurrent therapy as defined in the labeling for the drug" (21 CFR 300.50(a)). This has been interpreted to require a factorial analysis of proposed combination ingredients that demonstrates that the combination is more effective than each component of the combination alone. For HIV drugs, however, it would not be feasible or ethical to study the efficacy of an FDC in a clinical study with a factorial design in which the entire combination would be compared to its individual components. This type of study design would require HIV-infected individuals to be exposed to suboptimal regimens that could quickly result in drug resistance not only to the drug or drugs under study, but in many cases to other antiretroviral drugs from within the same class. Suboptimal therapy may jeopardize the success of future therapeutic options for those patients exposed to single or dual antiretroviral treatment. See section V for further information on showing efficacy of these combinations.

⁹ The list contains one triple-nucleoside analogue regimen.

¹⁰ Given the large number of potential combinations, it is not possible to study every possible regimen. For some combinations, extrapolated data from studies of similar combinations are considered to be supportive (although not necessarily sufficient). For example, stavudine + lamivudine is considered to offer potency similar to zidovudine + lamivudine in the setting of triple combinations with a protease inhibitor or NNRTI.

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- An acceptable risk-benefit profile, particularly for treatment-naive patients
- Preferred or alternative regimens for initiating antiretroviral therapy¹¹
- Lack of viral antagonism, overlapping toxicity, or inadequate efficacy between the two or three components in the FDC or co-packaged product

The list in Appendix B is not meant to be comprehensive and is expected to evolve as HIV clinical research continues. Applicants may have access to data supporting the efficacy and safety of combinations not included on this list. In advance of an NDA submission, sponsors should discuss with the Division of Antiviral Products the available support for an FDC or a co-packaged product.

Combinations of two or more active antiretroviral drugs such as those listed in Attachment B are not the only type of FDC product suitable for combinations. For example, Kaletra (lopinavir/ritonavir), an approved FDC, is an antiretroviral combined with a metabolic booster; a low dose of ritonavir (an inhibitor of cytochrome p450 3A) is used to increase plasma concentrations of lopinavir, the component responsible for the antiviral efficacy. Other HIV protease inhibitors are often administered with low doses of ritonavir and may be suitable for co-packaging or co-formulation. FDA encourages applicants to develop FDCs for this type of drug combination to help in simplifying regimens.

Antiretroviral drugs that should not be combined because of viral antagonism, overlapping toxicities, or poor virologic efficacy are listed in Attachment C.

V. CLINICAL CONSIDERATIONS

For many potential FDC or co-packaged products (e.g., those in Attachment B), FDA believes adequate clinical studies confirming safety and efficacy of the combination have already been conducted, obviating the need for new clinical studies. Applicants for FDC or co-packaged products may provide clinical efficacy and safety information by one or more of the following mechanisms:

- Referencing their own relevant NDA or IND submission
- Cross-referencing another applicant's submission for which they have been given right of reference
- Submitting peer-reviewed literature describing relevant clinical studies and other scientific information and a summary of information that provides the rationale for the combination

Before submitting an application, applicants should discuss with the Division of Antiviral Drug Products the clinical rationale and evidence to support a particular co-packaged product or FDC.

¹¹ See footnote 3.

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- Relying on FDA's findings of safety and effectiveness for approved drug products. This is subject to U.S. intellectual property rights and exclusivity for approval actions, so in some cases, a tentative approval may be the appropriate regulatory action.

We encourage applicants to discuss with FDA their plans for providing such information before making a submission.

In general, clinical support for an FDC or co-packaged product should include efficacy and safety data from at least one study, conducted under good clinical practices and evaluating changes in HIV-RNA and CD₄ cell counts for at least 48 weeks. Optimally, studies designed to demonstrate statistical noninferiority, or superiority, of the regimen to an accepted control regimen (at the time the study was conducted) are preferred. Other clinical studies evaluating components of the proposed regimen used in various triple combinations may help support the efficacy of the proposed triple regimen. In some cases, clinical support for a specific regimen can be based on well-controlled triple-combination studies that, when evaluated together, provide a convincing rationale for the proposed combination.

VI. CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS

For approval of new FDCs, it is important to determine that the rate and extent of absorption of each therapeutic moiety in an FDC product are the same as the rate and extent of absorption of each therapeutic moiety administered concurrently as separate single-ingredient products. For approval of FDCs for which reference products exist, applicants should show that the rate and extent of absorption of each component of the FDC are the same as those of each component of the U.S. reference listed FDC. This evaluation provides the link between the new combination drug product and the drug product(s) whose safety, efficacy, and quality parameters are well established. New bioavailability (BA) information for co-packaged approved drug products is not necessary. Drug-drug interaction studies should be conducted between the therapeutic components of the FDC or co-packaged products if the studies were not conducted previously, and the potential for an interaction cannot be ruled out.

For both 505(j) and 505(b)(2) applications, FDA's Center for Drug Evaluation and Research, Division of Scientific Investigations, routinely inspects the clinical and bioanalytical sites where the BE studies are conducted. Drug products will not be approved or tentatively approved without acceptable inspections.

The following section describes considerations related to the relative BA and BE evaluation of FDCs for HIV. For additional details, see the guidance for industry on *Bioavailability and Bioequivalence Studies for Orally Administered Drug Products — General Considerations*.

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If a BE study is conducted for higher strength products, a waiver of the requirement for a BE study for lower strength products may be obtained, based on proportional similarity and acceptable dissolution testing or the biopharmaceutics classification system. Refer to the guidance listed above and the guidance for industry on *Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System*. For FDC and co-packaged products, the waiver may be applicable when only one of the active components is of a lower strength.

A. Relative Bioavailability/Bioequivalence Study Design

The optimal study design is a randomized, single-dose, two-way crossover, in which subjects receive the FDC (test treatment) and the single entity products administered together (reference treatment), with an adequate washout between treatments.

The number of study subjects depends on the variability associated with the drug products studied. In most cases, 24 to 36 subjects will be adequate; however, studies should not include fewer than 12 subjects. If feasible, we recommend that sponsors enroll both male and female subjects.

B. Reference Drugs for Bioequivalence Studies

FDA strongly recommends that sponsors use the U.S.-approved drug as the reference drug in BE studies to support FDA approval of a new drug product. If the applicant has right of reference to information that shows that the brand name products in the United States and Europe are equivalent formulations, then a 505(b)(2) application could be approved based in part on a BE study conducted comparing the new product with the European approved product. The potential use of BE studies comparing a test drug with a European reference should be discussed with FDA in advance of any submission.

As stated previously, FDA will accept ANDAs for duplicates of U.S.-approved single-ingredient drug products and for the currently U.S.-approved FDCs. Under the Act, the proposed product described in the ANDA must establish bioequivalence to a product approved in the United States. Comparisons to other reference formulations for ANDAs are not acceptable. In addition, FDA recommends that applicants provide the manufacturing batch record for the FDC or co-packaged product used in the bioequivalence study. The bioequivalence batch should be a minimum of 100,000 dosage units or 10 percent of the intended commercial scale, whichever is greater, unless otherwise justified. In addition, 100 percent of the bioequivalence batch should be packaged.

C. Relevant Study Endpoints

The rate and extent of drug absorption are assessed by determining the following exposure measures: the area under the plasma concentration-time curve calculated to the

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last measured concentration (AUC_{0-t}) and extrapolated to infinity (AUC_{∞}), peak drug concentrations (C_{max}), and time to achieve peak drug concentrations (T_{max}).

D. Bioanalytical Method Validation

All bioanalytical methods should be well characterized, fully validated, and documented. In addition, assay precision and accuracy should be documented during analysis of samples collected during the relative BA/BE study. For additional details, see the guidance for industry on *Bioanalytical Method Validation*.

E. Data Analysis and Interpretation

Log-transformed AUC and C_{max} should be analyzed statistically using the analysis of variance procedure (ANOVA) and two one-sided tests. Only descriptive statistics are needed for T_{max} . A point estimate and 90 percent confidence interval should be calculated for the test/reference ratio for AUC and C_{max} . If the confidence intervals for AUC and C_{max} values for all active moieties fall entirely within the 80 to 125 percent boundaries, FDA considers the products to be bioequivalent. For NDAs only, in cases when all confidence intervals do not fall within 80 to 125 percent, applicants can submit exposure-response information to determine the clinical relevance of differences in exposure. For ANDAs, the 90 percent confidence intervals for AUC and C_{max} must fall entirely within the 80 to 125 percent boundaries.

F. Food Effect

For NDAs, it may be necessary to determine the effect of food on the absorption of the active moieties included in the combination product. For NDAs filed under section 505(b)(2), applicants are not required to conduct studies in both fed and fasted states. However, if the studies are only conducted under fasting conditions, the labeling will recommend that the product be administered without food. Applicants can contact the review division to discuss the need for a food effect study.

For ANDA (505(j)) applications, FDA requests a fasted single-dose BE study and a single-dose fed BE study in human subjects for each potential FDC, unless the RLD's FDA-approved labeling does not mention food effects on drug absorption or administration, or stipulates the drug must be given on an empty stomach.

For additional details about food-effect BA studies and fed BE studies, see the guidance for industry on *Food-Effect Bioavailability and Fed Bioequivalence Studies*.

G. Dissolution Testing

A discriminating dissolution method should be developed, with limits set, for each active pharmaceutical ingredient in a drug product. The dissolution method should be incorporated into the stability and quality control programs. Dissolution testing should

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ensure that the presence of two or more drugs does not affect the dissolution performance testing. For additional details, see the guidance for industry on *Dissolution Testing of Immediate Release Solid Oral Dosage Forms*. A single dissolution medium is desirable for an FDC product; however, that is not always achievable. For these cases, the use of a second medium can be important.

VII. CHEMISTRY, MANUFACTURING, AND CONTROLS

Developing a new FDC product poses formulation challenges, and it may be simpler from a development standpoint to co-package approved HIV drugs in blister packs, as long as the products have been shown to have the requisite stability for the proposed shelf life and to be safe and effective when used together. Co-packaged products are not limited to blister packs; other packaging may be appropriate and should be discussed with the division in advance.

There are two important CMC considerations for the review of FDC and co-packaged products: the manufacturing processes of the active pharmaceutical ingredients (APIs) and inspections. First, API manufacturing processes should be well documented through reference to the drug master files (DMFs) of the API suppliers unless complete data can be included in the application. Sponsors should ensure that DMFs are submitted to FDA for the process used in the manufacture of the APIs. Second, manufacturing, testing, packaging and labeling facilities for the drug product and the APIs should be available for inspection before approval to assess compliance with good manufacturing practices.

Because chemistry issues are different for co-packaged versus FDC products, they are addressed separately in subsections A and B below.

A. Applications Submitted for Co-Packaged Products

For products in integrated blister packaging (i.e., a blister strip or card containing multiple products), FDA expects that the individual products will already have been approved in the United States. In this situation, the CMC data will probably be available by cross-referencing another application or a drug master file¹² or could be readily generated.

The new information needed to support blister packaging is typically limited to stability data (21 CFR 314.50(d)(1)(ii)(a)) and includes limited accelerated and available long-term stability data.¹³ The application should include stability data on the drug product in the commercial packaging. For bulk containers, sponsors should collect stability data to determine a maximum holding time before final packaging, and should include that

¹² See 21 CFR 314.420.

¹³ See the guidance for industry *Q1A(R2) Stability Testing of New Drug Substances and Products*; International Conference on Harmonization.

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information in the application. Sponsors should also carry out appropriate stability studies on shipping containers, and these data should be available to FDA investigators conducting inspections, and to the reviewing division upon request. Assessment of stability includes assaying each active ingredient to meet acceptance criteria of 90 to 110 percent of labeled strength, determining individual and total impurity levels, and measuring dissolution rates. Data on moisture uptake in the dosage form should be available and may be especially important if the product is packaged in a blister container, because polymer/foil blisters are not as impervious to moisture as high-density polyethylene bottles or foil/foil blisters. Applicants should justify the proposed expiration dating period (e.g., supportive stability data, qualitative or statistical analysis of trends). Three co-packaging scenarios are described below in more detail.

1. For drugs that have previously been approved as stand-alone products in the United States in packaging identical to that used for the co-package, submission of an application with no new stability data on the co-packaged product may be possible. It may be appropriate to use comparative data (i.e., USP <671> moisture permeability) to support absence of stability data in the co-packaged application, with a commitment to report stability data for the co-packaged product after approval.
2. For drugs that have previously been approved as stand-alone products in the United States, but will be packaged differently for the co-packaged product, release and stability data from one batch of product should be provided. This batch should be at least 10 percent of the intended commercial scale, unless otherwise justified. We recommend that 1 to 3 months of long-term and accelerated stability data be available 1 month before approval, depending on whether the proposed packaging provides superior or equivalent protection compared to the previously approved packaging.
3. Some co-packaged products will not have been previously approved in the United States before submission for the PEPFAR program. In this situation, the recommendations given below in section B, Applications Submitted for FDCs, are generally appropriate.

FDA recommends that applicants submit stability data sets as they become available in the context of a rolling NDA under the fast track approval process. Postapproval extensions of the expiration dating period may be proposed as additional stability data become available.

Products distributed under the PEPFAR program are intended to be used in a number of countries with hot and dry or hot and humid conditions (climatic zones III and IV).¹⁴ Given the conditions that may be encountered during distribution and storage under programs such as PEPFAR, we recommend that firms generate data on the stability of their product under the conditions specified by regulatory authorities in the recipient nations and WHO. At the present time, it appears that long-term studies at 30 degrees Celsius/75% RH, and 6-month accelerated studies at 40 degrees Celsius/75% RH will cover use and registration in all climatic zones. To provide flexibility in sourcing of

¹⁴ See footnote 13.

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drugs for programs such as PEPFAR, firms may submit applications when they have sufficient stability data to support use in ICH climatic zones I and II (e.g., long-term data at 25 degrees Celsius/60% RH; accelerated at 40 degrees Celsius/75% RH).¹⁵ The data to support use in climatic zones III and/or IV could then be provided as an amendment to the application. Alternatively, firms could submit applications when they have sufficient stability data to support use in climatic zones III and IV. Data at 25 degrees Celsius/60% RH would not generally be important in this situation. Substitution of more stressful stability conditions will generally be acceptable to the FDA, and may avoid repetition of studies when alternative conditions are needed for registration in PEPFAR recipient nations.

B. Applications Submitted for FDCs

The following information on product quality, safety, and performance should be included in an application for FDCs. The recommendations given in sections B.2-B.7 are considered appropriate for single-ingredient dosage forms not previously approved in the United States that are being presented in new co-packaged combinations.

1. Data Showing Lack of Interaction Between Active Ingredients

One-time stress studies should be performed to identify potential products of reactions between active ingredients. We recommend that degradants likely to be present during manufacturing and storage be monitored during stability studies.

2. Appropriate Quality Standards for Each Active Ingredient and for the Dosage Form

Tests to be performed before release of each batch of drug substance and drug product (i.e., the specifications) and appropriate process controls during manufacture should be established.¹⁶

Validated analytical methods should be capable of distinguishing each active ingredient, synthesis (process) related impurities, and potential degradation products (see ICH Q6A).

If the active ingredients are poorly soluble and are present in the dosage form as discrete particles, consideration should be given to particle size control on drug substances, according to the criteria described in the ICH Q6A guidance. If these active ingredients can exist in different solid-state polymorphic forms, additional controls may be appropriate.

¹⁵ Dietz, R, K Feilner, F Gerst, and W Grimm, "Drug Stability Testing — Classification of Countries According to Climatic Zone," *Drugs Made in Germany*, 1993, 36:99-103.

¹⁶ Guidance for industry *Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances*; International Conference on Harmonization.

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Acceptance criteria for process impurities and degradants should be based on manufacturing experience and toxicological considerations. If impurities exceed the recommended qualification thresholds as described by relevant ICH guidance on drug substance¹⁷ and drug product,¹⁸ additional toxicological justification may be appropriate.

3. Assurance of Reproducible Drug Release From the Dosage Form

It is important to establish that each manufactured lot of the drug product releases all active ingredients at an appropriate rate. This is typically monitored by a dissolution test performed as part of the drug product specification. This test should use a physiologically relevant medium, one that can be correlated to an in vivo study, or a scientific justification for the dissolution medium (e.g., pH, composition) should be provided in the application. A single dissolution medium is desirable for an FDC product; however, this may not always be achievable. For these cases, the use of a second medium may appropriate.

4. Stability Data

Information about the drug substance manufacturing processes, facilities, and controls may be submitted either directly in the application or through a DMF. When new drug substance stability studies are appropriate because of a new manufacturing facility or a significant change in the process, the DMF may be submitted with 1-month stability data, and amended as additional data become available.

Applicants must demonstrate stability of the combination drug product (21 CFR 314.50 (d)(1)(ii)(a)), including accelerated and long-term stability data. The application should include stability data on the drug product in the commercial packaging. For bulk containers, sponsors should collect stability data to determine a maximum holding time before final packaging and should include that information in the application. Sponsors should also carry out appropriate stability studies on shipping containers, and these data should be available to FDA investigators conducting inspections, and to the reviewing division upon request. 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, and measuring dissolution rates. Data on moisture uptake in the dosage form should be submitted and are important if the product is to be packaged in a blister container, because polymer/foil blisters are not as impervious to moisture as high-density polyethylene bottles or foil/foil blisters. Adequate stability data should be provided for shelf-life determination, including justification for the proposed

¹⁷ Guidance for industry *Q3A (Revision 1) Impurities in New Drug Substances*; International Conference on Harmonization (<http://www.fda.gov/cder/guidance/4164fnl.doc>).

¹⁸ Guidance for industry *Q3B (Revision 1) Impurities in New Drug Products*; International Conference on Harmonization (<http://www.fda.gov/cder/guidance/5528fnl.doc>).

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expiration dating period (e.g., supportive stability data, qualitative or statistical analysis of trends).

Regarding the appropriate release and stability data, FDA anticipates that these applications will fall into one of the two different situations described below.

- (a) For antiretroviral drug products already marketed by the applicant in other countries or regions, where there are minor changes to the product in packaging, composition (e.g., coloring agents), or manufacturing site, FDA can accept less stability data if it is known from previous studies that the closely related product does not present stability problems. We recommend that 3 months of long-term and accelerated stability data be available 1 month before approval, although shorter data sets would also be considered when a very robust scientific link can be made to the supportive stability studies. A single batch is generally appropriate for this stability study, when accompanied by release and stability data on the supportive batches. This batch should be at least 10 percent of the intended commercial scale, unless otherwise justified. FDA recommends that applicants submit long-term and accelerated data from their own related product, and compare these to the data from the intended product. The relevance of the supportive stability data (e.g., packaging similar to the intended product; USP <671> moisture permeability) is taken into consideration when setting the expiration dating period.
- (b) If this is a new product or a new dosage form for the applicant, FDA recommends that 6 months of stability data under long-term and accelerated conditions be available 1 month before approval. These data should be obtained on at least two batches of drug product, manufactured by a process representative of the intended commercial process. At least one of these batches should be a minimum of 10 percent of the intended commercial scale, unless otherwise justified.

FDA recommends that applicants submit stability data sets as they become available in the context of a rolling NDA under the fast track approval process. Postapproval extensions of the expiration dating period may be proposed as additional stability data become available.

Products distributed under the PEPFAR program are intended to be used in a number of countries with hot and dry or hot and humid conditions (climatic zones III and IV).¹⁹ Given the conditions that may be encountered during distribution and storage under programs such as PEPFAR, we recommend that firms generate data on the stability of their product under the conditions specified by regulatory authorities in the recipient nations and WHO. At the present time, it appears that long-term studies at 30 degrees Celsius/75% RH, and 6-month accelerated studies at 40 degrees Celsius/75% HR will cover use and registration in all climatic zones. To provide flexibility in sourcing of drugs for programs such as PEPFAR, firms may submit

¹⁹ Deitz, R, K Feilner, F Gerst, and W Grimm, "Drug Stability Testing — Classification of Countries According to Climatic Zone," *Drugs Made in Germany*, 1993, 36:99-103.

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applications when they have sufficient stability data to support use in ICH climatic zones I and II (e.g., long-term data at 25 degrees Celsius/60% RH; accelerated at 40 degrees Celsius/75% RH).²⁰ The data to support use in climatic zones III and/or IV could then be provided as an amendment to the application. Alternatively, firms could submit applications when they have sufficient stability data to support use in climatic zones III and IV. Data at 25 degrees Celsius/60% RH would not generally be important in this situation. Substitution of more stressful stability conditions will generally be acceptable to the FDA, and may avoid repetition of studies when alternative conditions are needed for registration in PEPFAR recipient nations.

5. References or Data Supporting Safety of Excipients

Products should be formulated using excipients that meet internationally recognized compendial standards. Applicants should justify the use of novel excipients, using animal toxicity data if necessary.

6. Demonstration That the Manufacturing Processes for Active Ingredients and Dosage Form Are Defined and Understood

The manufacturing processes, including appropriate controls, should be described in the application for each drug substance and for the drug product (or provided by cross-referencing another application or a DMF²¹).

All applications, whether for integrated blister packaging or FDCs, should identify the manufacturing facilities where the active ingredients and the dosage forms are produced, packaged, and tested so that the FDA can verify that good manufacturing practices are followed appropriately.^{22,23}

At the time of inspections of API and finished dosage form manufacturing facilities, the master validation plan and results from at least one commercial-scale batch should be available. If the pilot and commercial equipment do not share the same operating principles, additional commercial-scale experience may be important. Results from the completed validation exercise can be sent to the Agency when they are available, and are not required before approval (or tentative approval).

It is valuable for FDA to receive information (e.g., method of manufacture, process controls, specification, and test results) about the specific antiretroviral drugs, as well

²⁰ Guidance for industry *Q1A(R2) Stability Testing of New Drug Substances and Products*; International Conference on Harmonization.

²¹ See 21 CFR 314.420 for additional information on referencing DMFs.

²² See 21 U.S.C. section 351(a)(2)(B); 21 CFR parts 210 and 211.

²³ Guidance for industry *Q7A Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients*; International Conference on Harmonization.

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as general information on other products produced in the facility, before inspections. Useful general information includes the type of operations carried out at the facility (e.g., synthesis of non-sterile API, fermentation, tablet manufacture), layout of the facility, address, and contact information. This information can be included in the DMF or as a submission to the application.

FDA will work with applicants on rapid evaluation of anticounterfeit technologies and approaches to minimize product diversion.²⁴

7. Selection of Packaging

Many applicants have expressed a preference for demonstrating the stability of their products in non-child-resistant packaging, which they anticipate will be most useful for programs such as PEPFAR. Issues related to special packaging (e.g., child-resistant and senior-friendly function) are best approached in the context of the recipient nations' regulations and prescribing practices. FDA is therefore willing to accept applications that include products packaged in bottles and blisters that applicants believe are acceptable to the regulatory authorities of the PEPFAR recipient nations. FDA could grant a tentative approval with this type of packaging. However, at the time of innovator patent expiry, when a tentative approval could be converted to a full marketing approval for the United States, the application should be amended to comply with all relevant U.S. packaging and labeling regulations.

If different packaging is selected after tentative approval, FDA anticipates that procurement organizations, applicants, and regulatory authorities will cooperate to share information on equivalence of protection.

VIII. MICROBIOLOGY/VIROLOGY

In general, FDC and co-packaged products containing approved antiretrovirals will require few, if any, additional nonclinical studies because data should usually be available from existing IND or NDA submissions, from literature references, or by reliance on FDA's findings for a previously approved drug. Any studies providing this type of data should have been conducted in accordance with accepted standards of good laboratory practices.

Applicants can submit virology data by:

- Referencing their own relevant NDA or IND submission
- Cross-referencing another applicant's submission for which they have been given right of reference

²⁴ See "Combating Counterfeit Drugs: A Report of the Food and Drug Administration," February 2004; http://www.fda.gov/oc/initiatives/counterfeit/report02_04.pdf.

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- Submitting peer-reviewed literature of relevant nonclinical studies, although this approach should be discussed in advance with the Division of Antiviral Drug Products
- Relying on the Agency's findings of safety and effectiveness for an approved drug

Specifically, the types of information that should be included or referenced to support an FDC are listed below. For drug combinations already supported by adequate clinical data, such as those mentioned in Attachment B, additional in vitro studies will not be needed.

- Mechanism of action of the individual components
- Antiviral activity in vitro against standard laboratory strains and clinical isolates (including a variety of the most common HIV clades from diverse geographic regions), and effects of serum protein binding on antiviral activity
- Cytotoxicity for dividing cells, including mitochondrial toxicity
- In vitro combination activity studies of the antiviral components to rule out antagonistic effects
- In vitro selection of resistant virus and phenotypic/genotypic characterization of the isolates. When components of the combination have the same target protein, selection of resistant virus in vitro should be carried out in the presence of the combination at concentrations equivalent to the in vivo concentrations. The genotypic and phenotypic nature of the resultant resistant isolates should be characterized to identify common resistance pathways.

FDC and co-packaged products should contain drugs that together impose a significant mutational barrier for the development of resistance. In clinical studies, some regimens consisting of three reverse transcriptase inhibitors have high virologic failure rates associated with high rates of drug resistance (see Attachment C). The cause of the high failure rates appears to be associated with the emergence of single or dual cross-resistant mutations that confer resistance to all three components.

IX. LABELING — PACKAGE INSERTS

For co-packaged products marketed in the United States, two options exist for package inserts:

- An integrated package insert containing information on each individual component contained in the co-packaged product
- Separate package inserts for each individual component of the co-packaged product

For FDC products, integrated package inserts are recommended.

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Particular safety issues are known for each of the combinations in Attachment B and should be addressed in labeling. Examples include nevirapine-associated rash, liver toxicity, and abacavir-associated hypersensitivity. Labeling for FDCs that include nevirapine should clearly state that the FDC is not appropriate for the first 2-week lead-in period of nevirapine use.

X. OTHER REGULATORY CONSIDERATIONS

A. Patients and Exclusivity

If the FDC and co-packaged products are developed by sponsors who either own or can obtain a sufficient right of reference to the underlying data, patents and exclusivity should not be a bar to the review and approval of such products. If these products are not developed by sponsors who either own or can obtain a right of reference to the underlying data, the regulations that govern the submission and approval of 505(j) and 505(b)(2) applications apply.

Approval could be delayed by applicable exclusivity (e.g., pediatric, 3-year, orphan), but the application could receive *tentative approval* (which recognizes that at the time the tentative approval action is taken, the application meets the technical and scientific requirements for approval, but final approval is blocked by patent or exclusivity). If one or more of the already-approved drugs has new chemical entity exclusivity, however, acceptance for review could be delayed.

If one or more of the approved drug components is covered by a patent, FDA cannot approve the 505(b)(2) or 505(j) application until the patent expires. If the patent is challenged by the 505(b)(2) or 505(j) applicant and the applicant is sued, the application could be approved after 30 months or when the patents are declared invalid or not infringed by a court, whichever is first. In the interim, the application could be tentatively approved.

FDC or co-packaged products that receive tentative approval are eligible for procurement under the PEPFAR program.

B. User Fees

By law, FDA must assess user fees on applications, products, and establishments that meet the legal criteria for fees (section 736(a) of the Act; 21 U.S.C. 379h(a)).²⁵ However, the law provides that under certain circumstances FDA can grant a waiver or reduction in fees. Potential waivers for FDC and co-packaged antiretrovirals are addressed in the

²⁵ The application fee, which must be paid at the time an application is submitted, is the most significant of the fees, totaling more than \$500,000.

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draft guidance for industry on *User Fee Waivers and Co-Packaged HIV Drugs for PEPFAR*.

For information about how to request a waiver or reduction, please contact the User Fee Team in the Office of Regulatory Policy at 301-594-2041. More information on user fees is available on the Internet at <http://www.fda.gov/cder/pdufa/default.htm>.

C. Pediatric Studies

The Pediatric Research Equity Act of 2003 (PREA) requires that pediatric studies be conducted for any new application (NDA, BLA, or supplement) that provides for a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration, unless the requirement is waived or deferred. Under PREA, pediatric studies may be deferred if (1) the drug is ready for approval 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 the applicant submits pertinent information to support the deferral. Pediatric studies can be fully waived if (1) the studies are impossible or impracticable, (2) there is evidence that the drug would be ineffective or unsafe in the pediatric population, or (3) the drug does not represent a meaningful therapeutic benefit over existing therapies and is not likely to be used in a substantial number of pediatric patients. We encourage applicants to consult FDA at the earliest possible time regarding their pediatric drug development plans and the availability of a waiver or deferral.

Waivers may be granted on a case-by-case basis for certain pediatric age groups for whom the doses in an FDC are not medically appropriate.

We also encourage applicants to consult the Agency about the availability of pediatric exclusivity under section 505A of the Act if applicants conduct studies requested by FDA that are needed to label the drug product for use in pediatric populations.

D. Postapproval Issues

Applicants are expected to comply with adverse event reporting requirements for an approved NDA (21 CFR 314.80 and 314.81) (i.e., reports of serious and unexpected adverse events within 15 days of receipt of the information by the applicant or its affiliates). If the combination product is to be mass distributed in developing countries, a system of collecting and reporting adverse drug reactions by the distributor would be desirable (e.g., through governmental or nongovernmental agencies distributing the products).

FDA will periodically reevaluate manufacturing facilities for PEPFAR applications that have received tentative approval, as is done for approved applications. Applicants should also file amendments to their applications to add additional manufacturing facilities or to add important new safety information to the labeling.

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ATTACHMENT A

SCENARIOS FOR APPROVAL OF FDC/CO-PACKAGED COMBINATIONS FOR TREATMENT OF HIV

Scenario 1: Two or more innovator companies agree to jointly develop a new drug application (NDA) for a two- or three-drug FDC or co-packaged product. Each of the individual component drug products is currently separately approved, and studies owned by one or more of the innovators show that the drugs are safe and effective when used together.

- Application is a *stand-alone* NDA under section 505(b)(1) of the Act, because the applicants of the FDC or co-packaged product own or have a right of reference to the underlying preclinical and safety and efficacy data for each of the individual component drug products and for the combination use on which the approval of the FDC or co-packaged product would be based.
- No new preclinical or safety and efficacy data are needed for the application because each of the products already is approved separately and studies owned by one or more of the innovators show that the products are safe and effective when used together.
- Bioavailability (BA) data are needed for FDCs to show that the combination product produces blood levels for each of the active ingredients adequate to achieve efficacy.
- The application contains chemistry data in accordance with the guidance, labeling, and other routine information.
- Approval would not be delayed by patents or most exclusivity. Only orphan exclusivity could delay an approval of a stand-alone NDA.²⁶
- If the applicant needs data or information from literature to support the safe and effective use of the combination, the application is not a stand-alone NDA (see Scenario 2).

Scenario 2: A non-innovator company wants to submit an application for approval of a new two- or three-drug fixed dose combination or co-packaged product with combined labeling or labeling showing how the drugs are used together. Each of the individual drug components is currently separately approved.

- If the non-innovator company does not own or have a right of reference to all preclinical and safety and efficacy data on the individual active ingredients and on the combination product, the application is an NDA described in section 505(b)(2) of the Act (505(b)(2) application). The application is not an abbreviated new drug

²⁶ For information on the orphan drug program, see <http://www.fda.gov/cder/handbook/orphan.htm>.

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application (ANDA) under section 505(j) because an ANDA requires the previous approval of a *reference listed drug* (RLD) (i.e., an approved product containing the same components for combination use).

- The application does not need to contain preclinical data or safety and efficacy data for the individual ingredients; however, safety and efficacy data for the combination, either from studies the non-innovator conducted or from the literature, are needed to support approval of the combination.
- BA data are needed to show that the combination product produces blood levels for each of the active ingredients adequate to achieve efficacy.
- The application contains chemistry, labeling, and other routine information.
- The applicable exclusivity (e.g., pediatric, 3-year, orphan) could delay approval, but the application could receive *tentative approval* (which recognizes that, at the time the tentative approval action is taken, the application meets the technical and scientific requirements for approval, but final approval is blocked by patent or exclusivity). If one or more of the already-approved drugs has new chemical entity exclusivity, however, acceptance for review could be delayed.
- If one or more of the approved drug components is covered by a patent, FDA cannot approve the 505(b)(2) application until the patent expires or, if the patent is challenged by the 505(b)(2) applicant and the applicant is sued, FDA cannot approve the application for 30 months or until the patents are declared invalid or not infringed by a court, whichever is first. However, the application could be tentatively approved.

Scenario 3: A non-innovator applicant wants to submit an ANDA under section 505(j) of the Act for approval of an already approved single-ingredient or two- or three-drug FDC product, such as the drug combinations approved in Combivir (zidovudine and lamivudine) or Trizivir (zidovudine, lamivudine, and abacavir).

- Under 505(j) of the Act, an ANDA must contain information to demonstrate that the proposed product is the same as the RLD (i.e., the FDA-approved single-ingredient or FDC product). However, if the non-innovator wants to submit an ANDA for a different route of administration, dosage form, or strength, or wants to substitute an equipotent dosage of one active ingredient for another of the same pharmacologic or therapeutic class in an FDC, the applicant may submit an ANDA suitability petition requesting authorization to do so. If it is determined that clinical safety or efficacy data are not needed to support the change, the petition will be approved and an ANDA can be submitted. The applicability of PREA would also be evaluated for petitions submitted for changes in route of administration, dosage form, or active ingredient. If PREA applies, the petition would not be approved because clinical safety or efficacy data are required for approval. PREA does not apply to petitions submitted for changes in strength. A 505(b)(2) application is an alternative route of submission for such changes.

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- An ANDA does not need to contain any preclinical data or clinical safety and efficacy data.
- The applicant must demonstrate that the proposed product is bioequivalent to the RLD (i.e., that the rate and extent of absorption of the active ingredient, or ingredients, are the same as that of the reference drug in accordance with certain statistical criteria).
- The application contains chemistry data, labeling, and other routine information.
- The applicable exclusivity (e.g., pediatric, 3-year, orphan) could delay approval, but the ANDA could receive *tentative approval* (which recognizes that, at the time the tentative approval action is taken, the application meets the technical and scientific requirements for approval, but final approval is blocked by patent or exclusivity). If the already-approved drug has new chemical entity exclusivity, however, acceptance for review could be delayed.
- If the approved listed drug is covered by a patent, FDA cannot approve the application until the patent expires. If the patent is challenged by the ANDA applicant and the applicant is sued, the application could be approved after 30 months or if the patent is declared invalid or not infringed by a court, whichever is first. In the interim, the application could be tentatively approved.

Scenario 4: An innovator company wants to give another company a license to obtain approval to market a single-ingredient, FDC, or co-packaged product.

- If the innovator provides a right of reference to all of the preclinical data and safety and efficacy data necessary for approval (see Scenario 1), the application is a stand-alone NDA under 505(b)(1).
- If an RLD exists (i.e., an approved product containing either the single ingredient or the same combination approved for the combination use), and the innovator does not provide a right of reference to the data (see Scenario 3), the application is an ANDA under section 505(j).
- If the data provided by the innovator are not adequate to support approval of the specific combination and the application must be supplemented with literature or other data (see Scenario 2), the application is a 505(b)(2) application.
- BA or BE data are needed, either to show that the single-ingredient or FDC product produces blood levels for each of the active ingredients adequate to achieve efficacy (for a stand-alone NDA or 505(b)(2) application) or that the rate and extent of absorption of the active ingredients are the same as the reference drug in accordance with certain statistical criteria (for an ANDA).

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- Patent rights and most exclusivity will not delay approval of a stand-alone NDA under 505(b)(1). Only orphan exclusivity could delay approval of a stand-alone NDA.
- As part of the patent certification process for an ANDA or 505(b)(2) application, the applicant provides evidence that the innovator company provided a license and agreed (1) not to exercise its patent rights and (2) to waive exclusivity.
- The application contains chemistry data, labeling, and other routine information.

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ATTACHMENT B

EXAMPLES OF TWO AND THREE HIV DRUG COMBINATIONS SUPPORTED BY CURRENT CLINICAL DATA

Two-drug combinations (to be used in combination with a third drug)

abacavir + lamivudine (approved FDC, trade name, Epzicom)
didanosine + lamivudine
didanosine + emtricitabine
stavudine + lamivudine
tenofovir + emtricitabine (approved FDC, trade name Truvada)
tenofovir + lamivudine
zidovudine + lamivudine (approved FDC, trade name Combivir)

Three-drug regimens^{27,28,29}

abacavir + lamivudine + efavirenz
abacavir + lamivudine + nelfinavir
abacavir + lamivudine + fosamprenavir
abacavir + lamivudine + fosamprenavir/ritonavir

didanosine + emtricitabine + efavirenz
didanosine + lamivudine + efavirenz

stavudine + lamivudine + atazanavir
stavudine + lamivudine + efavirenz
stavudine + lamivudine + lopinavir/ritonavir
stavudine + lamivudine + nelfinavir
stavudine + lamivudine + nevirapine

tenofovir + emtricitabine + efavirenz
tenofovir + lamivudine + efavirenz
tenofovir + emtricitabine + lopinavir/ritonavir

²⁷ Nevirapine is administered once daily for the first 2 weeks followed by twice daily. Therefore, for the first 2 weeks, a nevirapine-containing triple-regimen cannot be administered as a single FDC.

²⁸ Nelfinavir-based triple drug regimens are inferior to some other triple-drug regimens, but may have a role in treating pregnant women (Walmsley S, B Bernstein, M King, et al., "Lopinavir-Ritonavir Versus Nelfinavir for the Initial Treatment of HIV Infection," *N Engl J Med.*, 2002 Jun 27;346(26):2039-46. HHS Panel on Clinical Practice for the Treatment of HIV Infection, Guidelines for the Use of Antiretroviral Agents in HIV-1 Infected Adults and Adolescents, <http://www.aidsinfo.nih.gov/>; Yeni PG, SM Hammer, CC Carpenter, et al., "Antiretroviral Treatment for Adult HIV Infection in 2002: Updated Recommendations of the International AIDS Society-USA Panel," *JAMA*, 2002 Jul 10;288(2):222-35.

²⁹ Because of the different dosing schedules of the components, some triple combinations are more suitable for co-packaging than for FDCs.

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zidovudine + lamivudine + abacavir³⁰ (approved FDC, trade name TRIZIVIR)
zidovudine + lamivudine + efavirenz
zidovudine + lamivudine + lopinavir/ritonavir
zidovudine + lamivudine + nelfinavir
zidovudine + lamivudine + nevirapine
zidovudine + lamivudine + atazanavir

³⁰ Reported to be less potent than efavirenz-based HAART regimen (Gulick RM, HJ Ribaldo, CM Shikuma, et al., "Triple-Nucleoside Regimens Versus Efavirenz-Containing Regimens for the Initial Treatment of HIV-1 Infection," *N Engl J Med.*, 2004 Apr 29;350(18):1850-61).

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Label and Literature References for Two-Drug Antiretroviral Combinations

Combination (Dose Interval)	U.S. Reference Product	Clinical Reference from Approved Label(s) (Study)	Clinical Reference from Literature
abacavir + lamivudine <i>QD</i> <i>BID</i>	EPZICOM none	EPZICOM (CNA30021) EPZICOM (CNA30021) ZIAGEN (CNA30024) LEXIVA (APV30001: NEAT) (APV30002: SOLO)	Rodriquez-French JAIDS, 2004 ³¹ [Gathe AIDS 2004] ³²
didanosine + lamivudine ³³ <i>QD</i>	None	-- EMTRIVA (301A) (303)	Landman AIDS 2003 ³⁴ Saag 2004 ³⁵ Benson AIDS 2004 ³⁶
didanosine + emtricitabine <i>QD</i>	None	EMTRIVA (301A)	Saag 2004 ³⁷

³¹ Rodriguez-French A, J Boghossian, GE Gray, et al., “The NEAT Study: A 48-Week Open-Label Study to Compare the Antiviral Efficacy and Safety of GW433908 Versus Nelfinavir in Antiretroviral Therapy-Naive HIV-1-Infected Patients,” *J Acquir Immune Defic Syndr*. 2004 Jan 1;35(1):22-32.

³² Gathe JC Jr, P Ive, R Wood, et al., “SOLO: 48-Week Efficacy and Safety Comparison of Once-Daily Fosamprenavir /Ritonavir Versus Twice-Daily Nelfinavir in Naive HIV-1-Infected Patients,” *AIDS*. 2004 Jul 23;18(11):1529-37.

³³ Efficacy supported by literature reference and cross-study extrapolations from studies 301A and 303.

³⁴ Landman R, R Schiemann, S Thiam, “Once-a-Day Highly Active Antiretroviral Therapy in Treatment-Naive HIV-1-Infected Adults in Senegal,” *AIDS*. 2003 May 2;17(7):1017-22.

³⁵ Benson C, C van der Horst, A LaMarca, et al., “A Randomized Study of Emtricitabine and Lamivudine in Stably Suppressed Patients With HIV,” *AIDS*. 2004 Nov19;18(17):2269-76.

³⁶ See footnote 35.

Contains Nonbinding Recommendations

<p>stavudine + lamivudine</p> <p style="text-align: center;"><i>BID</i></p>	<p>None</p>	<p>--</p> <p>KALETRA (M98-863)</p> <p>REYATAZ (AI424-008)</p> <p>VIRACEPT (542)</p> <p>VIREAD (903)</p> <p>ZERIT (Start 1)</p>	<p>2NN [van Leth Lancet 2004]³⁸</p> <p>[Walmsley NEJM 2002]³⁹</p> <p>none</p> <p>none</p> <p>[Gallant JAMA 2004]⁴⁰</p> <p>[Squires, AIDS 2000]⁴¹</p>
<p>tenofovir + emtricitabine⁴²</p> <p style="text-align: center;"><i>QD</i></p>	<p>TRUVADA</p>	<p>VIREAD (903) (934)</p> <p>EMTRIVA (303)</p> <p>KALETRA (418)</p>	<p>[Gallant JAMA 2004]⁴³ [Gallant JAMA 2006]⁴⁴</p> <p>[Benson AIDS 2004]⁴⁵</p>

³⁷ Saag MS, P Cahn, F Raffi, et al., “Efficacy and Safety of Emtricitabine Versus Stavudine in Combination Therapy in Antiretroviral-Naive Patients: A Randomized Trial,” *JAMA*. 2004 Jul 14;292(2):180-9.

³⁸ van Leth F, P Phanuphak, K Ruxrungtham, et al. for the 2 NN Team, “Comparison of First-Line Antiretroviral Therapy With Regimens Including Nevirapine, Efavirenz, or Both Drugs, Plus Stavudine and Lamivudine: A Randomized Open-Label Trial, the 2NN Study,” *Lancet*. 2004;363:1253-63.

³⁹ Walmsley S, B Bernstein, M King, et al., “Lopinavir-Ritonavir Versus Nelfinavir for the Initial Treatment of HIV Infection,” *N Engl J Med*. 2002;346:2039-46.

⁴⁰ Gallant JE, S Staszewski, AL Pozniak, et al. for the 903 Study Group, “Efficacy and Safety of Tenofovir DF Versus Stavudine in Combination Therapy in Antiretroviral-Naive Patients: A 3-Year Randomized Trial,” *JAMA*. 2004;292:191-201

⁴¹ Squires KE, R Gulick, P Tebas, et al., “A Comparison of Stavudine Plus Lamivudine Versus Zidovudine Plus Lamivudine in Combination With Indinavir in Antiretroviral Naive Individuals With HIV Infection: Section of Thymidine Analog Regimen Therapy (START I),” *AIDS*. 2000;14:1591-1600.

⁴² Efficacy supported by cross-study extrapolation of studies 903 and 303.

Contains Nonbinding Recommendations

tenofovir + lamivudine <i>QD</i>	None	VIREAD (903)	[Gallant JAMA 2004] ⁴⁶
zidovudine + lamivudine <i>BID</i>	COMBIVIR	-- -- -- -- EPIVIR (EPV20001) REYATAZ (AI 424-034) SUSTIVA (006) VIDEX (AI-454-148) VIDEX EC (AI454-152) TRIZIVIR (CNAAB3005) ZIAGEN (CNAAB3005) (CNA30024) ZERIT (Start 1)	AACTG 384 [Shafer NEJM 2003] ⁴⁷ Combine [Podzamczar Antiviral Ther 2002] ⁴⁸ AACTG 5095 [Gulick NEJM 2004] ⁴⁹ CNA3014 [Vibhagool Cur Med Res Opin 2004] ⁵⁰ [Sension HIV Clin Trials 2002] ⁵¹ [Squires JAIDS 2004] ⁵² [Staszewski NEJM 1999] ⁵³ [Gathe JAIDS 2002] ⁵⁴ [Staszewski JAMA 2001] ⁵⁵ [Staszewski JAMA 2001] ⁵⁶ [Squires, AIDS 2000] ⁵⁷

⁴³ See footnote 37.

⁴⁴ Gallant, JE, E DeJesus, JR Arribas, et al. "Tenofovir DF, Emtricitabine, and Efavirenz vs. Zidovudine, Lamivudine, and Efavirenz for HIV." *N Engl J Med.* 2006;354(3):251-60.

⁴⁵ See footnote 33.

⁴⁶ See footnote 37.

⁴⁷ Shafer RW, LM Smeaton, GK Robbins, et al. for the ACTG 384 Team, "Comparison of Four-Drug Regimens and Pairs of Sequential Three-Drug Regimens as Initial Therapy for HIV-1 Infection," *N Engl J Med.* 2003;349:2304-15.

Contains Nonbinding Recommendations

**LABEL AND LITERATURE REFERENCES FOR THREE-DRUG
ANTIRETROVIRAL COMBINATION REGIMENS**

Combination (Dose Interval)	US Reference Product	Clinical Reference from Approved Label (Study)	Clinical Reference from Literature
abacavir + lamivudine + efavirenz <i>QD</i>	none	ZIAGEN (CNA30024)	none
abacavir + lamivudine + fosamprenavir			

⁴⁸ Podzamczar D, E Ferrer, E Consiglio, et al., “A Randomized Clinical Trial Comparing Nelfinavir or Nevirapine Associated to Zidovudine/Lamivudine in HIV-Infected Naive Patients (the Combine Study),” *Antivir Ther.* 2002;7:81-90.

⁴⁹ Gulick RM, HJ Ribaud, CM Shikuma, et al. for the ACTG A5095 Team, “Triple-Nucleoside Regimens Versus Efavirenz-Containing Regimens for the Initial Treatment of HIV-1 Infection,” *N Engl J Med.* 2004; 350:1850-61.

⁵⁰ Vibhagool A, P Cahn, M Schechter, et al., “Triple Nucleoside Treatment With Abacavir Plus the Lamivudine/Zidovudine Combination Tablet (COM) Compared to Indinavir/COM in Antiretroviral Therapy-Naive Adults: Results of a 48-Week Open-Label, Equivalence Trial (CAN 3014),” *Curr Med Res Opin.* 2004;20:1103-14.

⁵¹ Sension MG, NC Bellos, J Johnson, et al., “Lamivudine 300 mg QD Versus Continued Lamivudine 150 mg BID With Stavudine and a Protease Inhibitor in Suppressed Patients,” *HIV Clin Trials.* 2002;3:361-70

⁵² Squires K, A Lazzarin, JM Gatell, et al., “Comparison of Once-Daily Atazanavir With Efavirenz, Each in Combination with Fixed-dose Zidovudine and Lamivudine, As Initial Therapy for Patients Infected With HIV. *J Acquir Immune Defic Syndr.* 2004;36:1011-19.

⁵³ Staszewski S, J Morales-Ramirez, KT Tashima, et al., “Efavirenz Plus Zidovudine and Lamivudine, Efavirenz Plus Indinavir, and Indinavir Plus Zidovudine and Lamivudine in the Treatment of HIV-1 Infection in Adults. Study 006 Team.” *N Engl J Med.* 1999;341:1865-73.

⁵⁴ Gathe J, R Badaro, A Grimwood, et al., “Antiviral Activity of Enteric-Coated Didanosine, Stavudine and Nelfinavir Versus Zidovudine Plus Lamivudine and Nelfinavir,” *J Acquir Immune Defic Syndr.* 2002; 31:399-401.

⁵⁵ Staszewski S, P Keiser, J Montaner, et al. for the CNAAB3005 International Study Team. “Abacavir-Lamivudine-Zidovudine in Antiretroviral Naive HIV-Infected Adults: A Randomized Equivalence Trial,” *JAMA.* 2001; 285:1155-63.

⁵⁶ See footnote 49.

⁵⁷ See footnote 38.

Contains Nonbinding Recommendations

<i>BID</i> abacavir + lamivudine + fosamprenavir/ritonavir	none	LEXIVA (APV30001: NEAT)	[Rodriquez-French JAIDS, 2004] ⁵⁸
<i>QD</i>	none	LEXIVA (APV30002: SOLO)	[Gathe AIDS 2004] ⁵⁹
abacavir + lamivudine + nelfinavir <i>BID</i>	none	LEXIVA (APV30001: NEAT) (APV30002: SOLO)	[Rodriquez-French JAIDS, 2004] ⁶⁰ [Gathe AIDS 2004] ⁶¹
didanosine + emtricitabine + efavirenz <i>QD</i>	none	EMTRIVA (301A)	Saag 2004 ⁶²
didanosine + lamivudine + efavirenz <i>QD</i>	none	--	Landman 2003 ⁶³
stavudine + lamivudine + atazanvir <i>BID + QD (atazanvir)</i>	none	REYATAZ (AI424-008)	None
stavudine + lamivudine + efavirenz <i>BID + QD (efavirenz)</i>	none	-- VIREAD (903)	2NN [van Leth Lancet 2004] ⁶⁴
stavudine + lamivudine + lopinavir/ritonavir <i>BID</i>	none	KALETRA (M98-863)	[Walmsley NEJM 2002] ⁶⁵

⁵⁸ See footnote 30.

⁵⁹ See footnote 31.

⁶⁰ See footnote 30.

⁶¹ See footnote 31.

⁶² See footnote 34

⁶³ See footnote 32

⁶⁴ See footnote 35

Contains Nonbinding Recommendations

stavudine + lamivudine + nelfinavir <i>BID</i>	none	KALETRA (M98-863) REYATAZ (A1424-008) VIRACEPT (542)	[Walmsley NEJM 2002] ⁶⁶ none none
stavudine + lamivudine + nevirapine <i>BID</i>	none	--	2NN [van Leth Lancet 2004] ⁶⁷
tenofovir + emtricitabine + efavirenz ⁶⁸ <i>QD</i>	none	EMTRIVA (303) VIREAD (903) (934) TRUVADA (934)	[Benson AIDS 2004] ⁶⁹ [Gallant JAMA 2004] ⁷⁰ [Gallant NEJM 2006] ⁷¹ [Gallant NEJM 2006] ⁷²
tenofovir + emtricitabine + lopinavir/ritonavir <i>QD</i>	none	KALETRA (418)	
tenofovir + lamivudine + efavirenz <i>QD</i>	none	VIREAD (903)	[Gallant JAMA 2004] ⁷³

⁶⁵ See footnote 36

⁶⁶ See footnote 36.

⁶⁷ See footnote 35.

⁶⁸ Efficacy supported by cross-study extrapolation with studies 303 and 903.

⁶⁹ See footnote 33.

⁷⁰ See footnote 37.

⁷¹ See footnote 45.

⁷² See footnote 45.

⁷³ See footnote 37.

Contains Nonbinding Recommendations

<p>zidovudine + lamivudine + abacavir</p> <p style="text-align: center;"><i>BID</i></p>	<p>TRIZIVIR</p>	<p>-- --</p> <p>ZIAGEN (CNAAB3005) (CNA30024)</p> <p>TRIZIVIR (CNAAB3005)</p>	<p>AACTG 5095 [Gulick NEJM 2004]⁷⁴ CNA3014 [Vibhagool Cur Med Res Opin 2004]⁷⁵</p> <p>[Staszewski JAMA 2001]⁷⁶</p> <p>[Staszewski JAMA 2001]⁷⁷</p>
<p>zidovudine + lamivudine + efavirenz</p> <p style="text-align: center;"><i>BID + QD (efavirenz)</i></p>	<p>None</p>	<p>-- --</p> <p>EPIVIR (EPV20001)</p> <p>REYATAZ (AI 424-034)</p> <p>SUSTIVA (Dupont 006)</p> <p>ZIAGEN (CNA30024)</p>	<p>AACTG 384 [Shafer NEJM 2003]⁷⁸ AACTG 5095 [Gulick NEJM 2004]⁷⁹</p> <p>[Squires JAIDS 2004]⁸⁰</p> <p>[Staszewski NEJM 1999]⁸¹</p>
<p>zidovudine + lamivudine + lopinavir/ritonavir⁸²</p> <p style="text-align: center;"><i>BID</i></p>	<p>none</p>	<p>KALETRA</p>	

⁷⁴ See footnote 44.

⁷⁵ See footnote 45.

⁷⁶ See footnote 50.

⁷⁷ See footnote 50.

⁷⁸ See footnote 42.

⁷⁹ See footnote 44.

⁸⁰ See footnote 47.

⁸¹ See footnote 48.

Contains Nonbinding Recommendations

		(M98-863) ZERIT (Start 1)	[Walmsley NEJM 2002] ⁸³ [Squires, AIDS 2000] ⁸⁴
zidovudine + lamivudine + nelfinavir <i>BID</i>		-- -- VIDEX (AI-458-148) VIDEX EC (AI454-152)	AACTG 384 [Shafer NEJM 2003] ⁸⁵ Combine [Podzamczer Antiviral Ther 2002] ⁸⁶ [Gathe JAIDS 2002] ⁸⁷
zidovudine + lamivudine + nevirapine <i>BID</i>	none	--	Combine [Podzamczer Antiviral Ther 2002] ⁸⁸
zidovudine + lamivudine + atazanavir <i>BID + QD (atazanavir)</i>	none	REYATAZ (AI424-034)	[Squires JAIDS 2004] ⁸⁹

⁸² Efficacy supported by cross-study extrapolation with studies Start 1 and M98-863.

⁸³ See footnote 36.

⁸⁴ See footnote 38.

⁸⁵ See footnote 42.

⁸⁶ See footnote 43.

⁸⁷ See footnote 49.

⁸⁸ See footnote 43.

⁸⁹ See footnote 47.

Contains Nonbinding Recommendations

ATTACHMENT C

**COMBINATIONS FOR TREATMENT OF HIV NOT ACCEPTABLE
FOR FDC/COPACKAGING**

*Combinations with Viral Antagonism or Overlapping Toxicity*⁹⁰

stavudine + zidovudine
stavudine + zalcitabine
didanosine+zalcitabine

Combinations with Inadequate Efficacy

abacavir + lamivudine + tenofovir⁹¹
abacavir + emtricitabine + tenofovir⁹²
didanosine + lamivudine + tenofovir⁹³
didanosine + emtricitabine + tenofovir⁹⁴
didanosine + tenofovir plus another ARV (not recommended for treatment naive)

⁹⁰ See footnote 3.

⁹¹ Gallant JE, A Rodriguez, W Weinberg, et al., “Early Non-Response to Tenofovir DF (TDF) + Abacavir (ABC) and Lamivudine (3TC) in a Randomized Trial Compared to Efavirenz (EFV) + ABC + 3TC: ESS30009 Unplanned Interim Analysis.” Presented at the 43rd Interscience Conference on Antimicrobial Agents and Chemotherapy, Chicago, IL, September 16, 2003 (Abstract H-1722a).

⁹² See footnote 31.

⁹³ Jemsek J, P Hutcherson, E Harper, “Poor Virologic Responses and Early Emergence of Resistance in Treatment Naive, HIV-Infected Patients Receiving a Once Daily Triple Nucleoside Regimen of Didanosine, Lamivudine, and Tenofovir DF,” 11th Conference on Retroviruses and Opportunistic Infections, San Francisco, CA, February 2004.

⁹⁴ See footnote 34.