Guidance for Industry

Fixed Dose Combination and Co-Packaged Drug Products for Treatment of HIV

DRAFT GUIDANCE

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

May 2004

Procedural

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Fixed Dose Combination and Co-Packaged Drug Products for Treatment of HIV

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This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic.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 would be applied to such applications, what issues might be of concern, and how these 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) a sponsor plans to rely on literature or the FDA's findings of safety and effectiveness for an approved drug. Where appropriate, this guidance addresses the issues associated with these different scenarios.

For additional guidance, three attachments have been included: Attachment A contains some regulatory scenarios for approval of FDC or co-packaged products for the treatment of HIV. Attachment B contains examples of drug combinations supported by current clinical data and considered acceptable for FDC/co-packaging. Attachment C contains 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

[1] This guidance has been prepared by the Division of Anti-Viral 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.

cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

Combination therapy is essential for the treatment of HIV/AIDS. The goals of HIV therapy are to maximally and durably suppress 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 suppress the virus, allow recovery of the immune system, and reduce the emergence of HIV resistance. In the United States and developing countries, simplified HIV regimens in the form of co-packaged drugs (such as blister packs) or FDCs may facilitate distribution and improve patient adherence.

For treatment-naive patients (meaning those who are first initiating antiretroviral therapy), there are several preferred regimens outlined in the Department of Health and Human Services (HHS) treatment guidelines.[3] For treatment-experienced patients, the choice of combination regimens is more complex and individualized. Therefore, triple FDCs or co-packaged products are probably most useful for treatment-naive patients; however, this may change as treatment guidelines for treatment-experienced patients evolve.

Although there are more than 20 unique antiretroviral drugs approved in the United States under § 505 of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. § 355), only a few are approved for use as FDC products, and none is approved as a co-packaged product. Some antiretrovirals should not be combined due to overlapping toxicities and potential viral antagonism. Other antivirals should not be used in pregnant women and other special populations. It is important, therefore, that possible combinations of these products be evaluated for safety and efficacy in the various populations that may have need of them.

Recently, newer FDCs that have not been evaluated by the FDA have received attention, and some 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, the safety, efficacy, and quality of these products have not been evaluated by FDA. Products whose safety, efficacy, and quality do not

[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, 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.

[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.

conform to expected standards may pose a threat to individual patients by increasing the chances of substandard performance, which may lead not only to treatment failure, but also to the development and spread of resistant virus.

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

FDA recognizes that FDC and co-packaged products may also be valuable in the treatment of other serious infectious diseases such as tuberculosis and malaria. This guidance is being written to address issues in HIV therapy, although many of the principles relied upon are more generally applicable. Sponsors with potential products for other serious infections such as those just mentioned are invited to contact the Division of Anti-Viral Drug Products to discuss these proposals.

III. HIV THERAPY AND RESOURCE POOR SETTINGS

In his State of the Union address on January 28, 2003, President Bush announced the President's Emergency Plan for AIDS Relief that would provide $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 will play a major role in this relief plan, and it is important that resources spent on drug treatment be spent on treatments that have been demonstrated to be safe and effective.

On March 29 to 31, 2004, government officials and representatives of drug regulatory agencies from 23 nations, the research-based and generic pharmaceutical industries, public health leaders, healthcare providers, advocacy groups (including persons living with HIV/AIDS), academia, and members of nongovernmental organizations met to discuss the scientific and technical principles for FDC drug products for use in the treatment of AIDS, tuberculosis, and malaria, the most serious infectious disease threats facing the world today. On April 8, 2004, as a result of the meeting, the Southern African Development Community (SADC), the United Nations Joint Programme on HIV/AIDS (UNAIDS), HHS, and the World Health Organization (WHO) issued a joint statement titled Principles for Fixed-Dose Combination Drug Products.

The statement announced the development of a Principles Document addressing the development of FDCs and their potential benefits or disadvantages in treating these diseases. The Principles Document is to focus on aspects of the efficacy, safety, and quality of FDCs and provide points to consider when developing, evaluating, and/or considering FDC products for the treatment of these diseases. The document is not, however, intended to be a therapeutic or a regulatory guideline. A draft of the Principles Document was posted on the Internet on April 22, 2004,[5] and comments were solicited. A final draft of the document is being developed.

[5] See http://www.globalhealth.gov/fdc.shtml.

The FDA has determined that it would be useful to describe in more detail the U.S. regulatory pathway for the development of antiretroviral FDCs and co-packaged products as a way to encourage the development and approval of such products so that they will be available for the treatment and prevention of the global spread of HIV/AIDS.

IV. GENERAL CONSIDERATIONS

A. What Products Does this Guidance Apply To?

This guidance is aimed primarily at those combinations of individual drugs for antiretroviral therapy that have already been approved by the FDA for individual therapy and for which adequate evidence of safety and efficacy in combination already exists. We recommend that applicants contact the Division of Anti-Viral Drug Products with regard to combinations for which safety and effectiveness are not yet supported by currently available clinical data.

B. What Special Regulatory Procedures Are Available for FDC and Co-Packaged HIV Products?

Priority review and fast track designations are already available and likely would be applicable to these products. A priority review designation provides for the review of an application in 6 months or less.[6] We expect, however, that the applications described in this guidance could be reviewed within even shorter time frames.

Fast track designation offers a number of advantages that can facilitate drug development and approval (see the guidance for industry *Fast Track Drug Development Programs - Designation, Development, and Application Review*, September 1998). Fast track designation encompasses programs that were already in existence prior to 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 for 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 sponsors in the early development stages of either a co-packaged or FDC product to discuss the appropriateness of the combination, the dosing strength, and the appropriate nonclinical data.

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

The goal of having FDC or co-packaged HIV products is to simplify regimens to allow for 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

[6] FDA procedures have been established to address these designations (e.g., CDER MAPP 6020.3, *Priority Review Policy*).

potency and a sufficient barrier to the emergence of drug resistance. When developing FDCs or co-packaged products, we recommend that the products have the following important characteristics:

- Contain two or more components of a fully suppressive regimen
- Require a once or twice daily administration
- Be recommended as a preferred or alternate regimen (or regimen component) in treatment guidelines (see footnote 3)
- Have clinical efficacy and safety data that support use of the combination
- Be commonly used in treatment-naive patients
- Have drug interaction and toxicity profiles that allow for concomitant dosing

When considering proposed FDCs or co-packaged products, sponsors should take into account the required dosing frequency of each of the components. Each of the components of an FDC should have an 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. Applicants 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 guidelines[7] recommend preferred and alternate HIV treatment regimens for initial therapy. In general, recommended triple-treatment regimens consist of two drugs from the nucleoside (or nucleotide) reverse transcriptase inhibitor (NRTI) class and one drug from either the nonnucleoside reverse transcriptase inhibitor (NNRTI) class or protease inhibitor class. One triple-nucleoside FDC has been approved; however, in treatment guidelines, this regimen is recommended as an alternate regimen when other preferred regimens are not suitable.

As stated above, a large collection of clinical trial data and other scientific data (e.g., in vitro studies of resistance) have shown that it takes three active antiretrovirals to adequately sustain virologic control of HIV over the long term. It has also been shown that each antiretroviral in the type of combination regimens mentioned above contributes to the overall efficacy and potency of a regimen. 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 FDCs and co-packaged products, FDA has created a list of examples of regimens and regimen components (Attachment B) for which the clinical safety and efficacy of concomitant use have been evaluated and described in product labels or peer reviewed literature. FDA expects that developing FDCs or co-packaged products for

[7] See footnote 3.

combinations on this list could be accomplished without conducting new clinical efficacy and safety studies and that FDCs consisting of combinations on the attached list will satisfy the principles underpinning 21 CFR 300.50 with regard to their safe and effective use in combination.[8]

Inclusion criteria for this list are:

- Approved individual components
- Two-drug nucleoside analogue components[9] (to be used with a protease inhibitors 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 cells[10]
- Comparison of the regimen to appropriate controls
- Acceptable risk-benefit profile, particularly for treatment-naive patients
- Recommended as preferred or alternate regimens for initiating antiretroviral therapy.

This list is not meant to be comprehensive and will evolve over time as HIV clinical research continues.[11] Applicants may have access to data supporting the efficacy and safety of

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[8] 21 CFR 300.50 describes 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] This 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 similar potency as zidovudine + lamivudine in the setting of triple combinations with a protease inhibitor or NNRTI. Prior to submitting an application, applicants should discuss with the Division of Anti-Viral Drug Products the clinical rationale and evidence to support a particular co-packaged product or FDC.

[11] At this time, the list is limited to two- and three-component combinations. Several additional protease inhibitor-based regimens may be suitable for co-packaging or FDCs. However, since some of the protease inhibitor regimens require the addition of low-dose ritonavir, a fourth drug component would be required and may add complexity.

combinations not included on this list. Sponsors should discuss with the Division of Anti-Viral Drug Products, in advance of an NDA submission, the available support for a FDC or a co-packaged product.

There are antiretroviral drugs that should not be combined due to viral antagonism and overlapping toxicities. In addition, there are triple-combination regimens that have shown poor virologic efficacy, likely due to an inadequate mutational barrier against the emergence of resistance.[12] Drugs and regimens that would not be acceptable for FDCs or co-packaging because of known viral antagonism, poor virologic efficacy, or toxicity, are listed in Attachment C.

Combinations of two or more active antiretroviral drugs like 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 sponsors to develop FDCs for this type of drug combination to help in simplifying regimens.

V. CLINICAL CONSIDERATIONS

For many potential FDCs 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 that synthesizes the information and provides the rationale for the combination
- Relying on FDA's findings of safety and effectiveness for approved drug products, subject to U.S. intellectual property rights

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

[12] See footnote 3.

In general, clinical support for a FDC or co-packaged product should include efficacy and safety data from at least one well-controlled study for at least 48 weeks in duration evaluating changes in HIV-RNA and CD_4 cell counts. Optimally, the study should have been designed to demonstrate statistical noninferiority, or superiority, of the regimen to an accepted control regimen (at the time the study was conducted). In addition, other clinical studies evaluating components of the proposed regimen used in various triple combinations may help to support the efficacy of the proposed triple regimen. In some cases, clinical support for a regimen may be based on a collection of well-controlled triple-combination studies that, when evaluated together, provide a convincing rationale for the proposed combination.

VI. CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS

It is important to determine whether the rate and extent of absorption of each therapeutic moiety in a FDC product are the same as the rate and extent of absorption of each therapeutic moiety administered concurrently as separate single-ingredient products. This evaluation provides the link between the new combination drug product and the drug products whose safety, efficacy, and quality parameters are well established. It is unnecessary to provide new bioavailability information for co-packaged approved drug products. However, 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.

The following section describes considerations related to the relative bioavailability and bioequivalence evaluation of FDCs for HIV. For additional details, see the guidance for industry *Bioavailability and Bioequivalence Studies for Orally Administered Drug Products- General Considerations* (March 2003).

A. Relative Bioavailability/Bioequivalence Study Design

The optimal study design would be 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 subjects would depend on the variability associated with the drug products to be studied. In most cases, 24 to 36 subjects should be adequate. However, there should not be fewer than 12 subjects. If feasible, we recommend that both male and female subjects be enrolled.

B. Relevant Study Endpoints

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

C. 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 bioavailability/bioequivalence study. For additional details, see the guidance for industry *Bioanalytical Method Validation* (May 2001).

D. Data Analysis and Interpretation

We recommend that the AUC and C_{max} be analyzed statistically using the two one-sided tests procedure. Only descriptive statistics need to be determined for T_{max}. The AUC and C_{max} data are log-transformed prior to statistical testing. We recommend the statistical tests be implemented using the analysis of variance procedure (ANOVA). A point estimate and 90 percent confidence interval can 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, bioequivalence can be concluded. For NDAs only, in cases when all confidence intervals do not fall within 80 to 125 percent, it may be acceptable to use exposure-response information to determine the clinical relevance of differences in exposure.

E. 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. Sponsors can contact the review division to discuss the need for a food effect study.

For ANDA applications, it may be necessary to conduct separate fed and fasted bioequivalence studies.

For additional details about food-effect bioavailability studies and fed bioequivalence studies, see the guidance for industry *Food-Effect Bioavailability and Fed Bioequivalence Studies* (December 2002).

F. 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 ensure that the presence of two or more drugs does not affect the dissolution performance testing. For additional details, see the guidance for industry *Dissolution Testing of Immediate Release Solid Oral Dosage Forms* (August 1997).

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 be safe and effective when used together. Although the principles for establishing the safety and efficacy of an FDC also apply to co-packaged products, the chemistry issues are different.

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 have been already approved. In this situation, the needed chemistry, manufacturing, and controls (CMC) data would generally be available (by cross-referencing another application or a drug master file[13]) or could be generated readily.

The new information needed to support blister packaging would typically be limited to stability data (21 CFR 314.50 (d)(1)(ii)(a)). Data would typically include limited accelerated and available long-term stability data,[14] plus short-term stress studies under high temperature and/or high-humidity conditions.[15] Sponsors should evaluate the stability of the drug product in the actual dispensing package as well as in any bulk storage container and shipping container. Assessment of stability typically 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 to be packaged in a blister container, since polymer/foil blisters are not as impervious to moisture as high-density polyethylene bottles or foil/foil blisters. Justification should be provided for the proposed expiration dating period (e.g., supportive stability data, qualitative or statistical analysis of trends). The expiry period can generally be extended as additional stability data become available after approval.

B. Applications Submitted for FDCs

The application should generally include information covering the following aspects of product quality, safety, and performance.

1. Data showing lack of interaction between active ingredients

Typically, one-time stress studies should be performed to identify potential reaction products between active ingredients. We recommend that those 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

[13] See 21 CFR 314.420.

[14] Guidance for industry *Q1A(R2) Stability Testing of New Drug Substances and Products*; International Conference on Harmonization, November 2003.

[15] Guidance on *Q1F Stability Data Package for Registration Applications in Climatic Zones III and IV*; International Conference on Harmonization, November 2003.

Tests performed prior to 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. If the active ingredients are poorly soluble, controls for particle size should be in place. If these active ingredients can exist in different solid-state polymorphic forms, additional controls may be needed. Acceptance criteria for process impurities and degradants should be set based on manufacturing experience and toxicological considerations. If impurities exceed the recommended qualification thresholds,[17] additional toxicological justification may be necessary.

3. Assurance of reproducible drug release from the dosage form

It is important to establish that each manufactured lot of drug product will release 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.

4. Stability Data

Stability of the combination drug product needs to be demonstrated (21 CFR 314.50 (d)(1)(ii)(a)). Data would typically include accelerated and available long-term stability data,[18] plus short-term stress studies under high temperature and/or high humidity conditions (see ICH Q1F guidance). Sponsors should evaluate the stability of the drug product in the actual dispensing package as well as in any bulk storage container and shipping container. Assessment of stability typically 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 to be packaged in a blister container, since polymer/foil blisters are not as impervious to moisture as high-density polyethylene bottles or foil/foil blisters. Justification should be provided for the proposed expiration dating period (e.g., supportive stability data, qualitative or statistical analysis of trends). The expiry period can generally be extended as additional stability data become available after approval.

5. References or data supporting safety of excipients

[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, Deccember 2000.

[17] Guidance for industry *Q3B(R) Impurities in New Drug Products*; International Conference on Harmonization, November 2003.

[18] See guidance *Q1A(R2)*.

We recommend that the products be formulated using excipients that are described in internationally recognized compendia and meet these compendial standards. Justification for any novel excipients should be provided, including 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 drug master file[19]).

All applications, whether for integrated blister packaging or FDCs, should identify the manufacturing facilities where the active ingredients and the dosage form(s) are produced, packaged, and tested so that the FDA can verify that good manufacturing practices are followed appropriately.[20,21]

FDA will work with applicants on rapid evaluation of anti-counterfeit technologies.[22]

VIII. MICROBIOLOGY/VIROLOGY

In general, FDCs and co-packaged products containing approved antiretrovirals will require few, if any, additional nonclinical studies. Data from the following types of studies should usually be available from existing IND or NDA submissions, from literature references, or by reliance on the 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
- Submitting peer-reviewed literature of relevant nonclinical studies, although this approach should be discussed in advance with the Division of Anti-Viral Drug Products.
- Relying on the FDA's findings of safety and effectiveness for an approved drug

[19] See 21 CFR 314.420.

[20] FD&C Act § 501(a)(2)(B) (21 USC § 351(a)(2)(B); 21 CFR Part 210 and Part 211.

[21] Guidance for industry *Q7A Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients*; International Conference on Harmonization, August 2001.

[22] Combating Counterfeit Drugs: A Report of the Food and Drug Administration; February 2004; http://www.fda.gov/oc/initiatives/counterfeit/report02_04.pdf.

Specifically, the types of information that should be included or referenced to support an FDC are listed below. However, 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.

FDCs and co-packaged products should contain drugs that together impose a significant mutational barrier for the development of resistance. In clinical studies, some triple-nucleoside regimens have been shown to 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. ADVERSE EVENT REPORTING

Applicants are expected to comply with 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).

X. OTHER REGULATORY CONSIDERATIONS

A. Patents and Exclusivity

If these FDC and co-packaged products are to be developed by sponsors who either own or can obtain a 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 would apply. In these

situations, the FDA encourages the applicant to contact the review division to discuss possible approaches to the development of their product(s).

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 FD&C Act, 21 U.S.C. 379h(a)).[23] However, the law provides that under certain circumstances FDA can grant a waiver or reduction in fees.

The waiver criteria provide that FDA may grant a waiver or reduction in fees for any of the following reasons:

- A waiver or reduction is necessary to protect the public health.
- Assessment of the fee would present a significant barrier to innovation because of limited resources available to such person or other circumstances.
- The fees to be paid by such person will exceed the anticipated present and future costs incurred by the Secretary in conducting the process for the review of human drug applications for such person.[24]
- The applicant involved is a small business submitting its first human drug application to the Secretary for review.[25]

FDA is evaluating the circumstances under which it may grant user fee waivers or reductions for sponsors developing products under this guidance.

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 appropriate information to support the deferral. Pediatric studies may 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

[23] The application fee, which must be paid at the time an application is submitted, is the most significant of the fees, representing over $500,000.

[24] For a complete discussion of the fees-exceed-the-costs waiver provision, see FDA's guidance document entitled Fees-Exceed-the-Costs Waivers Under the Prescription Drug User Fee Act.

[25] See section 736(d)(3), 21 U.S.C. 379h(d)(3), of the Act for the rules for small business waivers.

a meaningful therapeutic benefit over existing therapies and it is not likely to be used in a substantial number of pediatric patients. FDA encourages sponsors to consult with FDA at the earliest possible time regarding their pediatric drug development plans and the availability of a waiver or deferral.

FDA also encourages sponsors to consult with the FDA regarding the availability of pediatric exclusivity under § 505A of the FD&C Act if sponsors conduct studies requested by FDA that are needed to label the drug product for use in pediatric populations.

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 there are studies owned by one or more of the innovator sponsors showing that the drugs can be safely and effectively used together.

- Application would be a *stand alone* NDA under section 505(b)(1) of the FD&C Act, because the sponsors of the FDC or co-packaged product would 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.

- Because each of the products already is separately approved and there are studies owned by one or more of the innovator sponsors showing that the products can be safely and effectively used together, no new preclinical or safety and efficacy data would be needed for the application.

- Bioavailability data would be needed for FDCs to show that the combination product would produce blood levels for each of the active ingredients adequate to achieve efficacy.

- The application would contain chemistry data per the guidance, labeling, and other routine information.

- Approval would not be delayed by patents or most exclusivity. Approval of a stand alone NDA could be delayed only by orphan exclusivity.[26]

- If the sponsor needs data or information from literature to support the safe and effective use of the combination, the application would not be a stand alone NDA (see scenario 2).

Scenario 2: A noninnovator 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 showing how the drugs should be used together. Each of the individual drug components is currently separately approved.

- The application would be an NDA described in section 505(b)(2) of the FD&C Act (a 505(b)(2) application) if the noninnovator 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. It cannot be an abbreviated new drug application (ANDA) under section 505(j) because an ANDA would require the previous approval of a *reference listed drug* (i.e., an approved product containing the same components for the combination use).

[26] For information on the Orphan Drug program, see http://www.fda.gov/cder/handbook/orphan.htm.

- The application does not need to contain preclinical data or safety and efficacy data for the individual ingredients, but would have to provide safety and efficacy data for the combination, either from studies the noninnovator conducted or from the literature, to support approval of the combination.

- Bioavailability data would be needed to show that the combination product will produce blood levels for each of the active ingredients adequate to achieve efficacy.

- The application would contain chemistry data per the guidance, labeling, and other routine information.

- Approval could be delayed by applicable exclusivity (e.g., pediatric, three-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, the FDA could not 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, 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 noninnovator applicant wants to submit an ANDA under section 505(j) of the FD&C 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).

- An ANDA would have to demonstrate that the proposed product is the same as the approved single-ingredient or FDC product. If the noninnovator wants to substitute one ingredient for another in a FDC, it can submit a suitability petition requesting authorization to do so.

- 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 reference listed drug (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 would contain chemistry data, labeling, and other routine information.

- Approval could be delayed by applicable exclusivity (e.g., pediatric, three-year orphan), 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, we could not approve the application until the patent expired or, if the patent is challenged by the ANDA applicant and the applicant is sued, for 30 months or until the patent is declared invalid or not infringed by a court, whichever is first. However, 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.

- The application would be a stand alone NDA under 505(b)(1) if the innovator provided a right of reference to all of the preclinical data and safety and efficacy data necessary for approval (see scenario 1).

- The application would be an ANDA under section 505(j) if there is a reference listed drug (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 would be a 505(b)(2) application if the data provided by the innovator are not adequate to support approval of the specific combination and application must be supplemented with literature (see scenario 2).

- Bioavailability or bioequivalence data would be needed, either to show that the single ingredient or fixed combination product will produce blood levels for each of the active ingredients adequate to achieve efficacy (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 that of the reference drug in accordance with certain statistical criteria (an ANDA).

- 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 would provide evidence that the innovator company has provided a license and has agreed not to exercise its patent rights and that the innovator has agreed to waive exclusivity.

- The application would contain chemistry data, labeling, and other routine information.

ATTACHMENT B: EXAMPLES OF COMBINATIONS FOR TREATMENT OF HIV SUPPORTED BY CURRENT CLINICAL DATA FOR FDC/CO-PACKAGING

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

abacavir + lamivudine
didanosine[27] + lamivudine
didanosine[27] + emtricitabine
stavudine + lamivudine
tenofovir + emtricitabine
tenofovir + lamivudine
zidovudine + lamivudine (approved FDC, trade name Combivir)

Three-drug regimens

abacavir + lamivudine + lopinavir/ritonavir
abacavir +lamivudine + nevirapine[28]
abacavir + lamivudine + efavirenz

didanosine[27] + emtricitabine + efavirenz
didanosine[27] + lamivudine + efavirenz

stavudine + lamivudine + efavirenz
stavudine + lamivudine + lopinavir/ritonavir
stavudine + lamividine + nelfinavir[29]
stavudine + lamivudine + nevirapine[28]

tenofovir + emtricitabine + efavirenz
tenofovir + lamivudine + efavirenz

zidovudine + lamivudine + abacavir[30] (approved FDC, trade name Trizivir)
zidovudine + lamivudine + efavirenz[31]

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[27] A once-daily formulation would facilitate dosing.

[28] Nevirapine is administered once daily for the first two weeks followed by twice daily. Therefore, for the first two weeks, one could not administer the triple-regimen as a single FDC.

[29] Nelfinavir-based 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).

[30] Reported to be less potent than efavirenz-based HAART regimen (Gulick RM, HJ Ribaudo, 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).

[31] Because of different dosing schudules, this would be more suitable for co-packaging.

715 zidovudine + lamivudine + lopinavir/ritonavir
716 zidovudine + lamivudine + nelfinavir
717 zidovudine + lamivudine + nevirapine[28]

ATTACHMENT C: COMBINATIONS FOR TREATMENT OF HIV NOT ACCEPTABLE FOR FDC/CO-PACKAGING

Combinations with Viral Antagonism or Overlapping Toxicity[32]

stavudine + zidovudine
stavudine + zalcitabine
didanosine+zalcitabine

Combinations with Inadequate Efficacy[32]

abacavir + lamivudine (or emtricitabine) + tenofovir
didanosine + lamivudine (or emtricitabine) + tenofovir

[32] See footnote 3.