Guidance for Industry

Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees

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

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User Fees

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This guidance 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. An alternative approach may be used if such 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 describes FDA's current thinking on what will be considered a separate marketing application and what will constitute clinical data for purposes of the user fee provisions of the Federal Food, Drug, and Cosmetic Act (Act).[2]

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

The Act levies a user fee on each "human drug application" including applications (1) for approval of a new drug submitted under section 505(b)(1) after September 1, 1992; (2) for approval of a new drug submitted pursuant to section 505(b)(2) after September 30, 1992, for certain molecular entities or indications for a use; and (3) for licensure of certain biological products under section 351 of the Public Health Service Act submitted after September 1, 1992.[3]

[1] This guidance has been prepared by the User Fee Staff in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration (FDA) in consultation with the Center for Biologics Evaluation and Research (CBER).

[2] The Prescription Drug User Fee Act was originally enacted in 1992, was amended in 1997 by the Food and Drug Administration Modernization Act, and was amended in June 2002 by the Prescription Drug User Fee Amendments of 2002.

[3] Section 735(1) (21 U.S.C. 379g(1)).

The Act provides for different user fees for original applications depending upon whether they are accompanied by clinical data on safety and/or efficacy (other than bioavailability or bioequivalence studies).[4] The Act also levies fees on supplements to human drug applications that require clinical data.[5] Under the fee schedules provided in the Act, original applications without clinical data and supplements that require clinical data are assessed approximately one-half the fee of original applications. This guidance for industry discusses (1) what should be contained in separate marketing applications and what should be combined into one application (*bundling guidance*) for purposes of assessing user fees and (2) the definition of *clinical data* for purposes of assessing user fees.

Because different user fees are assessed for original applications and supplements, FDA believes it is useful to provide guidance to applicants on the Agency's interpretation of what constitutes a separate original application, amendment, or supplement.

We recommend that a potential applicant consider this guidance when preparing an application or supplement. If FDA determines that an application has been inappropriately bundled, or that an applicant has incorrectly concluded that an application did not contain clinical data, then FDA will notify the applicant and request additional fees, if appropriate. This action will not prevent the filing of the application if it is otherwise suitable for filing, or its review, if it is otherwise ready for review. If an applicant disagrees with the determination, the applicant may formally appeal such disputes to the Office or Center level.[6]

III. PRESCRIPTION DRUG USER FEE BUNDLING POLICY

The factors currently considered by CDER and CBER in determining whether separate applications should be submitted and assessed separate fees are described below. Section A contains the guidance for original applications, and Section B contains guidance on supplements. The Agency may, for administrative reasons (e.g., review across two divisions or offices), assign separate reference numbers and separately track and take regulatory action on the various parts of what is considered to be one application under the policy described here.

[4] Section 736(a)(1) and (b) (21 U.S.C. 379(a)(1) and (b)). Bioavailability/bioequivalence studies are applicable only to applications submitted under section 505 of the Federal Food, Drug, and Cosmetic Act. They are not addressed in section 351 of the Public Health Service Act.

[5] Section 736(a)(1) (21 U.S.C. 379h(a)(1)).

[6] FDA's guidance for industry, *Formal Dispute Resolution: Appeals Above the Division Level*, February 2000.

A. Original Applications and Amendments

1. Different Active Ingredients or Combinations of Active Ingredients or Products

a. Drugs

Every different active ingredient[7] or combination of two or more different active ingredients should be submitted in a separate original application. Products to be marketed as both a racemic mixture and a single enantiomer should be in separate original applications. Similarly, drug substances purified from mixtures with multiple constituents of an active ingredient (e.g., enantiomers) should also be in separate original applications.

b. Biological Products

A biological product is identified in section 351 of the Public Health Service Act (42 U.S.C. 262(i)) as "any virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, or analogous product . . . applicable to the prevention, treatment, or cure of a disease or condition of human beings." The Act describes those biologicals that are assessed user fees.[8]

Individual biological product applications can include a single or combination biological product meeting the above definition, which would result in the issuance of a distinct product license. New applications for combination biological products should be submitted when any one of the constituents of the combination is altered in a manner that, for some other reason described in this guidance, warrants a separate application.

2. Different Routes of Administration

Products to be administered using different routes of administration (see FDA's *Approved Drug Products with Therapeutic Equivalence Evaluations* (the Orange Book) Appendix C) should be submitted in separate original applications unless the product(s) for use by all routes in a given application are quantitatively and qualitatively identical (drugs) or alike (biological products) in composition (e.g., an injectable liquid dosage form intended for use by the intravenous and intraperitoneal routes).

3. Different Dosage Forms

Different dosage forms (see the Orange Book, Appendix C) should be submitted in separate original applications unless the products are identical (drugs) or alike (biological products) in quantitative and qualitative composition (e.g., a sterile liquid in a single dose vial that is intended for use as either an injectable or an inhalation solution).

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[7] For example, different salts, esters, and complexes of the same active moiety are considered to be different active ingredients.

[8] Section 735(1) of the Act (21 U.S.C. 379g(1)).

4. Different Strengths/Concentrations

Different strengths or concentrations of one drug substance, active biological product, or combination product, if they are the same dosage form intended for the same route of administration and the same general indication(s), should be submitted in one original application if their qualitative composition is identical (drugs) or alike (biologicals).

5. Excipients

Single entity or combination products with excipients that differ qualitatively or quantitatively to accommodate different container sizes and configurations, or that differ qualitatively or quantitatively with respect to colors, flavorings, adjustment of pH or osmolality, or preservatives,[9] should be submitted in a single original application unless, for some other reason described in this guidance or elsewhere, a separate application is warranted. Differences in excipients that require separate clinical studies of safety or effectiveness should not be included in the same original application. Differences in excipients in topical products that require separate in vivo demonstration of bioequivalence should be included in separate original applications.

6. Container Sizes and Configurations

Different container sizes and configurations (e.g., filled syringes, ampules, sealed vials) of one finished pharmaceutical product intended to be for the same route of administration for the same indication(s) (or otherwise consistent with sections II.A.2 and II.A.3 above), should be considered one application for purposes of assessing user fees.

7. Different Indications or Claims

If submitted simultaneously in one application, requests for approval of different indications and uses for the same dosage form to be administered by the same route of administration (or otherwise consistent with sections II.A.2 and II.A.3, above) can be regarded, for the purposes of assessing user fees, as one application regardless of:

- the dose to be administered;
- the duration of use;
- the schedule of administration;
- the population in which the product is indicated; or
- the condition for which the product is indicated.

[9] Identical products in both single- and multiple-dose vials with and without preservatives can be submitted in a single application, provided that data are included demonstrating the same clinical activity of the two presentations.

After initial submission, a pending original or supplemental application should not be amended to add a new indication or claim. Previously submitted indications or claims can be modified by, for example, reanalyses of previously submitted data or, in rare instances, supplementary clinical data. Such amendments could result in subsequent adjustments to the user fee review clock. Submitting new clinical or in vitro data to support a new claim(s) to an already submitted original application during the review of that application is not recommended. Such a submission would be considered developing the product on the review clock and is contrary to the spirit and intent of the Act.

If the original application is not yet approved, a request for approval of other new indications or claims should be submitted in a separate, original application. If the initial application is approved, the application can be subsequently supplemented to add a new indication. (See section II.B. on supplemental applications.) At the time of submission, an original application should be complete and ready for a comprehensive review.

8. Medicare Modernization Act Changes

The Medicare Prescription Drug, Improvement, and Modernization Act of 2003[10] may require a new application to be submitted because of a change to the reference listed drug. If there are no other material changes to the new application, other than to specify the new reference listed drug, a fee may not be required consistent with the user fee exception for previously filed applications.[11]

B. NDA and BLA Supplements

1. Changes in Composition

We recommend that a change in the composition of an approved product to support a change in the dosage form or route of administration (other than those discussed in section I.A.2 or I.A.3 above) should be submitted as a separate original application.

2. Other Changes to Approved Products

A change to an approved product based on chemistry, manufacturing, or controls data and bioequivalence, or other studies (e.g., safety and immunogenicity), that changes (1) the strength or concentration; (2) the manufacturing process, equipment, or facility; or (3) the formulation (e.g., different excipients) can be submitted as a supplement to an approved application. Such a change would not ordinarily warrant a new original application unless it changes the dosage form or route of administration (see sections I.A.2 and I.A.3, above).

3. Changes to Indications

[10] Public Law 108-173.

[11] Section 736(a)(1)(C) of the Act (21 U.S.C. 379h(a)(1)(C)).

A request for approval of a new indication, or a modification of a previously approved indication, should be submitted individually in a separate supplement to an approved original application.[12]

The Agency does not recommend that new clinical or in vitro data, submitted in support of a new indication or claim, other than that required in safety updates be submitted as part of the pending supplement during the review of a given supplemental application. Such a submission would be considered developing the product on the review clock and is contrary to the spirit and intent of the Act. Previously submitted indications or claims can, however, be modified by, for example, reanalyses of previously submitted data, or, in rare instances, supplementary clinical data.

FDA recommends the basic operating principle that, at the time of submission, a supplement should be complete and ready for a comprehensive review. Modifications of the supplement should be only to clarify part of the already submitted supplement or to answer specific questions raised by the review team. FDA does not recommend that modifications expand or broaden the scope of the already submitted supplement unless they are requested by the Agency.

IV. DEFINITION OF CLINICAL DATA

Original applications and supplements may be accompanied by data reporting clinical experience in humans. However, not all such reports of experience in humans are regarded by the FDA as *clinical data* for purposes of assessing user fees. The term c*linical data,* for purposes of assessing user fees, encompasses a broad range of studies that are purported to be adequate and well-controlled investigations submitted in support of approval.

User fees will be assessed for original applications (NDAs or BLAs) and supplements containing the following types of clinical data required to form the primary basis for approval:

- Study reports or literature reports of what are explicitly or implicitly represented by the applicant to be adequate and well-controlled trials for safety or effectiveness; or
- Reports of comparative activity (other than bioequivalence and bioavailability studies), immunogenicity, or efficacy, where those reports are necessary to support a claim of comparable clinical effect.

For purposes of assessing user fees, FDA does not consider the following to meet the definition of clinical data:

- Individual case reports describing experience in clinical use submitted in support of a labeling change to add adverse reactions;

[12] The Act states, "The term *supplement* means a request to the Secretary to approve a change in a human drug application which has been approved" (21 U.S.C. 379g(2)). Each indication is considered a separate change, for which a separate supplement should be submitted. FDA can then approve each indication when it is ready for approval, rather than delaying approval until the last of a group of indications is ready to be approved.

- Data used to modify the labeling to add a restriction that would improve the safe use of the drug (e.g., to add an adverse reaction, contraindication, or warning to the labeling);
- Data from bioequivalence studies or studies of bioavailability of a drug submitted in supplements to NDAs, even if the studies include clinical endpoints; or
- Safety, biochemical equivalence, and/or limited comparative product equivalence data used to support BLA supplements for manufacturing process or site changes.