Guidance for Industry

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

Additional copies are available from:

Office of Training and Communications
Division of Communications Management
Drug Information Branch, HFD-210
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane, Rockville, MD 20857
(Tel) 301-827-4573
http://www.fda.gov/cder/pdufa/default.htm

Office of Communication
Training, and Manufacturers Assistance (HFM-40)
Center for Biologics Evaluation and Research (CBER)
1401 Rockville Pike, Rockville, MD 20852-1448
http://www.fda.gov/cber/guidelines.htm
(Fax) 888-CBERFAX or 301-827-3844
(Voice Information) 800-835-4709 or 301-827-1800

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)

December 2000
User Fees
Revision 1

TABLE OF CONTENTS

Guidance for Industry[1]

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

This draft guidance, when finalized, will represent the Food and Drug Administration's current thinking on this topic.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If you plan to submit comments on this draft guidance, to expedite FDA review of your comments, please:

- *Clearly explain each issue/concern and, when appropriate, include a proposed revision and the rationale/justification for the proposed change.*
- *Identify specific comments by line number(s); use the PDF version of the document, whenever possible.*

I. INTRODUCTION

This guidance describes FDA's current policy regarding what will be considered a separate marketing application and what will constitute clinical data for purposes of the User Fee Act.

The Prescription Drug User Fee Act (User Fee Act)[2] 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) under 505(b)(2) submitted after September 30, 1992, for certain molecular entities or indications for use; (3) for initial certifications or approvals of antibiotic drugs submitted under section 507 after September 1, 1992; and (4) for licensure of certain biological products under section

[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). This guidance originally was developed and issued prior to the publication of the Agency's regulation on good guidance practices (GGPs) (21 CFR 10.115; 65 FR 56468, September 19, 2000). This revision is being issued to delete prior Appendices A and B, to direct readers to the book "Approved Drug Products with Therapeutic Equivalence Evaluations" (the Orange Book) for a listing of dosage forms and routes of administration, and to make it consistent with the GGP regulation.

[2] The User Fee Act was originally enacted in 1992 and was renewed in 1997.

351 of the Public Health Service Act submitted after September 1, 1992.[3]

The User Fee Act provides for different user fees for original applications depending upon whether they are accompanied by clinical data on safety and efficacy (other than bioavailability or bioequivalence studies).[4] The Act also levies fees on supplements to human drug applications that contain clinical data.[5] Under the fee schedules provided in the User Fee Act, original applications without clinical data and supplements with 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.

A potential applicant should consider this guidance when it prepares its application or supplement. FDA expects to follow this guidance in assessing applications in the foreseeable future to determine whether an application is appropriate for filing. If FDA determines that an application has been inappropriately bundled, or that an applicant incorrectly concluded that an application did not contain clinical data, FDA will notify the applicant and request additional fees, if appropriate. This will not prevent the filing of the application if the application 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 appeal through appeal procedures to be established later in each Center and, subsequently, to the Ombudsman.

II. FDA BUNDLING POLICY

Because different user fees will be assessed on 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.

CDER and CBER policy for determining whether separate applications will be accepted is described below. Section A contains the guidance for original applications and Section B contains guidance on supplements. Nevertheless, 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.

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

[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)).

A. Original Applications and Amendments[6]

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, polymorphs) 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 User Fee Act describes those biologicals subject to User Fees.

Individual biological product applications may 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 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).

[6] Original application ordinarily means a complete new filing (NDA or BLA) for an applicant. If related but separate applications are submitted, the second and subsequent applications in a series may cross-reference appropriate sections in the initial submission.

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

3. Different Dosage Forms

Different dosage forms (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).

4. Pharmacy Bulk Packages and Products for Prescription Compounding (CDER)

Pharmacy bulk packages and products for prescription compounding should be submitted as separate original applications and should have their own package insert.

5. 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).

6. 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,[8] should be submitted in a single original application unless for some other reason described in this guidance, 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.

[8] 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.

7. Container Sizes and Configurations

Except for pharmacy bulk packs (see section A.4, above), 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 items 2 and 3 above), should be considered one application for purposes of assessing user fees.

8. 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 items 2 and 3, above) may 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.

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. New clinical or in vitro data to support a new claim(s) should not be submitted to an already submitted original application during the review of that application. Such a submission would be considered tantamount to developing the product on the review clock and is contrary to the spirit and intent of the User Fee Act.

If the original application is not yet approved, a request for approval of other new indications or claims could be submitted in a separate, original application. If the initial application is approved, the application then can be supplemented to add a new indication. See section II.B. on supplemental applications. The basic operating principle should be that, at the time of submission, an original application should be complete and ready for a comprehensive review.

B. NDA and BLA Supplements

1. Changes in Composition

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. 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) should 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 items I.A.2 and I.A.3, above).

3. Changes to Indications

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.[9]

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

The basic operating principle should be 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. Modifications should not be to expand or broaden the scope of the already submitted supplement unless they are requested by the agency.

[9] The User Fee 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. The policy allows FDA to 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.

III. DEFINITION OF CLINICAL DATA

Many different types of applications and supplements may be accompanied by data reporting clinical experiences in humans. Not all such reports of experience in humans are regarded by FDA as *clinical data* for purposes of assessing user fees. For example, FDA does not consider individual case reports describing experience in clinical use submitted in support of a labeling change to add adverse reactions to be *clinical data* under the User Fee Act. *Clinical data* 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; 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, *clinical data* do not include 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).

Supplements to new drug applications based solely on bioequivalence studies or studies of bioavailability of a drug are not considered to contain clinical data for purposes of assessing user fees, even if the studies include clinical endpoints.

Supplements to biological license applications in support of a process or site change that use safety, biochemical equivalence, and/or limited comparative product equivalence data generated in animals or humans as the supportable basis for such a change are not considered to contain clinical data for the purposes of assessing user fees.