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

DRAFT GUIDANCE

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For questions regarding this draft document contact Mike Jones (CDER) 301-594-2041, or Carla Vincent (CBER) 301-827-3503.

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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Guidance for Industry

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Division of Communications Management
Drug Information Branch, HFD-210
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Food and Drug Administration
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*Office of Communication
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Center for Biologics Evaluation and Research (CBER)
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(Fax) 888-CBERFAX or 301-827-3844
(Voice Information) 800-835-4709 or 301-827-1800*

**U.S. Department of Health and Human Services
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Center for Biologics Evaluation and Research (CBER)**

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Guidance for Industry¹

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This draft guidance, when finalized, will represent the Food and Drug Administration's current thinking on this topic.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If you plan to submit comments on this draft guidance, to expedite FDA review of your comments, please: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

35 351 of the Public Health Service Act submitted after September 1, 1992.³

36
37 The User Fee Act provides for different user fees for original applications depending upon whether they
38 are accompanied by clinical data on safety and efficacy (other than bioavailability or bioequivalence
39 studies).⁴ The Act also levies fees on supplements to human drug applications that contain clinical data.⁵

40 Under the fee schedules provided in the User Fee Act, original applications without clinical data and
41 supplements with clinical data are assessed approximately one-half the fee of original applications. This
42 guidance for industry discusses: (1) what should be contained in separate marketing applications and
43 what should be combined into one application (*bundling guidance*) for purposes of assessing user fees;
44 and (2) the definition of *clinical data* for purposes of assessing user fees.

45
46 A potential applicant should consider this guidance when it prepares its application or supplement.
47 FDA expects to follow this guidance in assessing applications in the foreseeable future to determine
48 whether an application is appropriate for filing. If FDA determines that an application has been
49 inappropriately bundled, or that an applicant incorrectly concluded that an application did not contain
50 clinical data, FDA will notify the applicant and request additional fees, if appropriate. This will not
51 prevent the filing of the application if the application is otherwise suitable for filing, or its review, if it is
52 otherwise ready for review. If an applicant disagrees with the determination, the applicant may appeal
53 through appeal procedures to be established later in each Center and, subsequently, to the
54 Ombudsman.

55 56 57 **II. FDA BUNDLING POLICY**

58
59 Because different user fees will be assessed on original applications and supplements, FDA believes it is
60 useful to provide guidance to applicants on the agency's interpretation of what constitutes a separate
61 original application, amendment, or supplement.

62
63 CDER and CBER policy for determining whether separate applications will be accepted is described
64 below. Section A contains the guidance for original applications and Section B contains guidance on
65 supplements. Nevertheless, the Agency may, for administrative reasons (e.g., review across two
66 divisions or offices), assign separate reference numbers and separately track and take regulatory action
67 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)).

69 **A. Original Applications and Amendments⁶**

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71 **1. *Different Active Ingredients or Combinations of Active Ingredients, or Products***

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73 **a. Drugs**

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75 Every different active ingredient⁷ or combination of two or more different active
76 ingredients should be submitted in a separate original application. Products to be
77 marketed as both a racemic mixture and a single enantiomer should be in separate
78 original applications. Similarly, drug substances purified from mixtures with multiple
79 constituents of an active ingredient (e.g., enantiomers, polymorphs) should also be in
80 separate original applications.

81
82 **b. Biological Products**

83
84 A biological product is identified in section 351 of the Public Health Service Act (42
85 U.S.C. 262(i)), as "any virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood
86 component or derivative, allergenic product, or analogous product . . . applicable to the
87 prevention, treatment, or cure of a disease or condition of human beings." The User
88 Fee Act describes those biologicals subject to User Fees.

89
90 Individual biological product applications may include a single or combination biological
91 product meeting the above definition, which would result in the issuance of a distinct
92 product license. New applications for combination biological products should be
93 submitted when any one of the constituents of the combination is altered in a manner
94 that for some other reason described in this guidance, warrants a separate application.

95
96 **2. *Different Routes of Administration***

97
98 Products to be administered using different routes of administration (see the Orange Book,
99 Appendix C) should be submitted in separate original applications unless the product(s) for use
100 by all routes in a given application are quantitatively and qualitatively identical (drugs) or alike
101 (biological products) in composition (e.g., an injectable liquid dosage form intended for use by
102 the intravenous and intraperitoneal routes).

103

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.

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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.

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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.

174 **B. NDA and BLA Supplements**

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176 *1. Changes in Composition*
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178 A change in the composition of an approved product to support a change in the dosage form or
179 route of administration (other than those discussed in section I.A.2 or I.A.3 above) should be
180 submitted as a separate original application.

181
182 *2. Changes to Approved Products*
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184 A change to an approved product, based on chemistry, manufacturing or controls data and
185 bioequivalence or other studies (e.g., safety and immunogenicity) that changes (1) the strength
186 or concentration; (2) the manufacturing process, equipment, or facility; or (3) the formulation
187 (e.g., different excipients) should be submitted as a supplement to an approved application.
188 Such a change would not ordinarily warrant a new original application unless it changes the
189 dosage form or route of administration (see items I.A.2 and I.A.3, above).

190
191 *3. Changes to Indications*
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193 A request for approval of a new indication, or a modification of a previously approved
194 indication, should be submitted individually in a separate supplement to an approved original
195 application.⁹

196
197 New clinical or in vitro data, submitted in support of a new indication or claim other than that
198 required in safety updates should not be submitted as part of the pending supplement during the
199 review of a given supplemental application. Such a submission would be considered tantamount
200 to developing the product on the review clock and is contrary to the spirit and intent of the User
201 Fee Act. Previously submitted indications or claims may, however, be modified by, for
202 example, reanalyses of previously submitted data or, in rare instances, supplementary clinical
203 data.

204
205 The basic operating principle should be that, at the time of submission, a supplement should be
206 complete and ready for a comprehensive review. Modifications of the supplement should be
207 only to clarify part of the already submitted supplement or to answer specific questions raised
208 by the review team. Modifications should not be to expand or broaden the scope of the already
209 submitted supplement unless they are requested by the agency.

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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.

212 **III. DEFINITION OF CLINICAL DATA**

213

214 Many different types of applications and supplements may be accompanied by data reporting clinical
215 experiences in humans. Not all such reports of experience in humans are regarded by FDA as *clinical*
216 *data* for purposes of assessing user fees. For example, FDA does not consider individual case reports
217 describing experience in clinical use submitted in support of a labeling change to add adverse reactions
218 to be *clinical data* under the User Fee Act. *Clinical data* encompasses a broad range of studies that
219 are purported to be adequate and well-controlled investigations submitted in support of approval.

220

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

223

- 224 • study reports or literature reports of what are explicitly or implicitly represented by the
225 applicant to be adequate and well-controlled trials; or
- 226
- 227 • reports of comparative activity (other than bioequivalence and bioavailability studies),
228 immunogenicity, or efficacy, where those reports are necessary to support a claim of
229 comparable clinical effect.

230

231 For purposes of assessing user fees, *clinical data* do not include data used to modify the labeling to
232 add a restriction that would improve the safe use of the drug (e.g., to add an adverse reaction,
233 contraindication, or warning to the labeling).

234

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

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