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Guidance for Industry

Applications Covered by Section 505(b)(2)

DRAFT GUIDANCE

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For questions on the content of the draft document contact Virginia Beakes, (301) 594-2041.

U. S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
October 1999

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For additional copies, contact:

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

U.S. Department of Health and Human Services
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GUIDANCE FOR INDUSTRY[1]

Applications Covered by Section 505(b)(2)

I. WHAT IS THE PURPOSE OF THIS GUIDANCE?

This guidance identifies the types of applications that are covered by section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (the Act). A 505(b)(2) application is a new drug application (NDA) described in section 505(b)(2) of the Act. It is submitted under section 505(b)(1) of the Act and approved under section 505(c) of the Act. This guidance also provides further information and amplification regarding FDA's regulations at 21 CFR 314.54.

Section 505 of the Act describes three types of new drug applications: (1) an application that contains full reports of investigations of safety and effectiveness (section 505(b)(1)); (2) an application that contains full reports of investigations of safety and effectiveness but where at least some of the information required for approval comes from studies not conducted by or for the applicant and for which the applicant has not obtained a right of reference (section 505(b)(2)); and (3) an application that contains information to show that the proposed product is identical in active ingredient, dosage form, strength, route of administration, labeling, quality, performance characteristics, and intended use, among other things, to a previously approved product (section 505(j)). Note that a supplement to an application is a new drug application.

Section 505(b)(2) was added to the Act by the Drug Price Competition and Patent Term Restoration Act of 1984 (Hatch-Waxman Amendments). This provision expressly permits FDA to rely, for approval of an NDA, on data not developed by the applicant. Sections 505(b)(2) and (j) together replaced FDA's *paper NDA policy*, which had permitted an applicant to rely on studies published in the scientific literature to demonstrate the safety and effectiveness of duplicates of certain post-1962 pioneer drug products (see 46 FR 27396, May 19, 1981). Enactment of the generic drug approval provision of the Hatch-Waxman Amendments ended the need for approvals of duplicate drugs through the paper NDA process by permitting approval under 505(j) of duplicates of approved drugs (listed

[1]This guidance has been prepared by the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration. This guidance document represents the Agency's current thinking on the types of applications that may be submitted pursuant to section 505(b)(2) of the Act. 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 statute, regulations, or both.

drugs) on the basis of chemistry and bioequivalence data, without the need for evidence from literature of effectiveness and safety. Section 505(b)(2) permits approval of applications other than those for duplicate products and permits reliance for such approvals on literature or on an Agency finding of safety and/or effectiveness for an approved drug product.

Definitions for specific terms used throughout this guidance are given in the Glossary.

II. WHAT IS A 505(B)(2) APPLICATION?

A 505(b)(2) application is one for which one or more of the investigations relied upon by the applicant for approval "were not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted" (21 U.S.C. 355(b)(2)).

A. What type of information *can* an applicant rely on?

What type of information can an applicant rely on in an application that is based upon studies "not conducted by or for the applicant and for which the applicant has not obtained a right of reference?"

1. Published literature

An applicant should submit a 505(b)(2) application if approval of an application will rely to any extent on published literature (a *literature-based* 505(b)(2)). If the applicant has not obtained a right of reference to the raw data underlying the published study or studies, the application is a 505(b)(2) application; if the applicant obtains a right of reference to the raw data, the application may be a full NDA (i.e., one submitted under section 505(b)(1)). An NDA will be a 505(b)(2) application if any of the specific information necessary for approval is obtained from literature or from another source to which the applicant does not have a right of reference, even if the applicant also conducted clinical studies to support approval. Note, however, that this does not mean ***any*** reference to published general information (e.g., about disease etiology, support for particular endpoints, methods of analysis) or to general knowledge causes the application to be a 505(b)(2) application. Rather, reference should be to specific information (clinical trials, animal studies) necessary to the approval of the application.

2. The Agency's finding of safety and effectiveness for an approved drug

An applicant should submit a 505(b)(2) application for a change in a drug when approval of the application relies on the Agency's previous finding of safety and/or effectiveness for a drug. This mechanism, which is embodied in a regulation at 21 CFR 314.54, essentially makes the Agency's conclusions that would support the approval of

a 505(j) application available to an applicant who develops a modification of a drug. Section 314.54 permits a 505(b)(2) applicant to rely on the Agency's finding of safety and effectiveness for an approved drug to the extent such reliance would be permitted under the generic drug approval provisions at section 505(j). This approach is intended to encourage innovation in drug development without requiring duplicative studies to demonstrate what is already known about a drug while protecting the patent and exclusivity rights for the approved drug.

It is possible that an applicant could submit a 505(b)(2) application that relies both on literature and upon the Agency's finding of safety and effectiveness for a previously approved drug product (e.g., to support a new claim).

B. What kind of application can be submitted as a 505(b)(2) application?

1. New chemical entity (NCE)/new molecular entity (NME)

A 505(b)(2) application may be submitted for an NCE when some part of the data necessary for approval is derived from studies not conducted by or for the applicant and to which the applicant has not obtained a right of reference. For an NCE, this data is likely to be derived from published studies, rather than FDA's previous finding of safety and effectiveness of a drug. If the applicant had a right of reference to all of the information necessary for approval, even if the applicant had not conducted the studies, the application would be a considered a 505(b)(1) application.

2. Changes to previously approved drugs

For changes to a previously approved drug product, an application may rely on the Agency's finding of safety and effectiveness of the previously approved product, coupled with the information needed to support the change from the approved product. The additional information could be new studies conducted by the applicant or published data. This use of section 505(b)(2), described in the regulations at 21 CFR 314.54, was intended to encourage innovation without creating duplicate work and reflects the same principle as the 505(j) application: it is wasteful and unnecessary to carry out studies to demonstrate what is already known about a drug. The approach was described in a letter to industry dated April 10, 1987, from Dr. Paul D. Parkman, then Acting Director of the Center for Drugs and Biologics. This guidance helps to clarify and amplify the approaches stated in the April 10, 1987, letter and in the regulations.

An applicant should file a 505(b)(2) application if it is seeking approval of a change to an approved drug that would not be permitted under section 505(j), because approval will require the review of clinical data. However, section 505(b)(2) applications should

not be submitted for duplicates of approved products that are eligible for approval under 505(j) (see 21 CFR 314.101(d)(9)).

In addition, an applicant may submit a 505(b)(2) application for a change in a drug product that is eligible for consideration pursuant to a suitability petition under Section 505(j)(2)(C) of the Act. In the preamble to the implementing regulations for the Hatch-Waxman amendments to the Act, the Agency noted that an application submitted pursuant to section 505(b)(2) of the Act is appropriate even when it could also be submitted in accordance with a suitability petition as defined at section 505(j)(2)(C) of the Act (see 57 FR 17950; April 28, 1992).

III. WHAT ARE SOME EXAMPLES OF 505(B)(2) APPLICATIONS?

Following are examples of changes to approved drugs for which 505(b)(2) applications should be submitted. Please note that in particular cases, changes of the type described immediately below may not require review of information other than BA or BE studies or data from limited confirmatory testing.[2] In those particular cases, approval of the drug may also be sought in a 505(j) application based on an approved suitability petition as described in section 505(j)(2)(C) of the Act. The descriptions below address the situation in which the application should be filed as a 505(b)(2) application because approval of the application will require review of studies beyond those that can be considered under section 505(j). Some or all of the additional information could be provided by literature or reference to past FDA findings of safety and effectiveness for approved drugs, or it could be based upon studies conducted by or for the applicant or to which it has obtained a right of reference.

- *Dosage form.* An application for a change of dosage form, such as a change from a solid oral dosage form to a transdermal patch, that relies to some extent upon the Agency's finding of safety and/or effectiveness for an approved drug.

- *Strength.* An application for a change to a lower or higher strength.

- *Route of administration.* An application for a change in the route of administration, such as a change from an intravenous to intrathecal route.

- *Substitution of an active ingredient in a combination product.* An application for a change in one of the active ingredients of an approved combination product for another active ingredient that has or has not been previously approved.

Following are additional examples of applications that may be accepted pursuant to section 505(b)(2) of the Act. Some or all of the additional information could be provided by the literature or reference to

[2] Limited confirmatory testing is explained in further detail in 54 FR 288872, 28880 (July 10, 1989) and 57 FR 17950, 17957-58 (April 28, 1992).

past FDA findings of safety and effectiveness for approved drugs, or it could be based on studies conducted by or for the applicant or to which it has obtained a right of reference.

- *Formulation.* An application for a proposed drug product that contains a different quality or quantity of an excipient(s) than the listed drug where the studies required for approval are beyond those considered limited confirmatory studies appropriate to a 505(j) application.

- *Dosing regimen.* An application for a new dosing regimen, such as a change from twice daily to once daily.

- *Active ingredient.* An application for a change in an active ingredient such as a different salt, ester, complex, chelate, clathrate, racemate, or enantiomer of an active ingredient in a listed drug containing the same active moiety.

- *New molecular entity.* In some cases a new molecular entity may have been studied by parties other than the applicant and published information may be pertinent to the new application. This is particularly likely if the NME is the prodrug of an approved drug or the active metabolite of an approved drug. In some cases, data on a drug with similar pharmacologic effects could be considered critical to approval.

- *Combination product.* An application for a new combination product in which the active ingredients have been previously approved individually.

- *Indication.* An application for a not previously approved indication for a listed drug.

- *Rx/OTC switch.* An application to change a prescription (Rx) indication to an over-the-counter (OTC) indication.

- *OTC monograph.* An application for a drug product that differs from a product described in an OTC monograph (21 CFR 330.11), such as a nonmonograph indication or a new dosage form.

- *Naturally derived or recombinant active ingredient.* An application for a drug product containing an active ingredient(s) derived from animal or botanical sources or recombinant technology where clinical investigations are necessary to show that the active ingredient is the same as an active ingredient in a listed drug.

- *Bioinequivalence.* Generally, an application for a pharmaceutically equivalent drug product must be submitted under section 505(j) of the Act and the proposed product must be shown to be bioequivalent to the reference listed drug (21 CFR 314.101(d)(9)). Applications for proposed drug products where the rate (21 CFR 314.54(b)(2)) and/or extent (21 CFR 314.54(b)(1)) of absorption exceed, or are otherwise different from, the 505(j) standards for bioequivalence compared to a listed drug may be submitted pursuant to section 505(b)(2) of the

Act. Such a proposed product may require additional clinical studies to document safety and efficacy at the different rate and extent of delivery. Generally, the differences in rate and extent of absorption should be reflected in the labeling of the 505(b)(2) product. The proposed product does not need to be shown to be clinically *better* than the previously approved product; however, a 505(b)(2) application should not be used as a route of approval for poorly bioavailable generic drug products unable to meet the 505(j) standards for bioequivalence. If the proposed product is a duplicate of an already approved product, it should not be submitted as a 505(b)(2) application (21 CFR 314.101(d)(9)).

For example, a 505(b)(2) application would be appropriate for a controlled release product that is bioinequivalent to a reference listed drug where:

1. The proposed product is at least as bioavailable as the approved pharmaceutically equivalent product (unless it has some other advantage, such as smaller peak/trough ratio); or

2. The pattern of release of the proposed product, although different, is at least as favorable as the approved pharmaceutically equivalent product.

IV. WHAT CAN'T BE SUBMITTED AS 505(B)(2) APPLICATIONS?

- An application that is a duplicate of a listed drug and eligible for approval under section 505(j) (see 21 CFR 314.101(d)(9)); or,

- An application in which the *only* difference from the reference listed drug is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than the listed drug (21 CFR 314.54(b)(1)); or,

- An application in which the *only* difference from the reference listed drug is that the rate at which its active ingredient(s) is absorbed or otherwise made available to the site of action is *unintentionally* less than that of the listed drug (21 CFR 314.54(b)(2)).

V. WHY DOES IT MATTER IF AN NDA IS A 505(B)(2) APPLICATION?

Unlike a full NDA for which the sponsor has conducted or obtained a right of reference to all the data essential to approval, the filing or approval of a 505(b)(2) application may be delayed due to patent or exclusivity protections covering an approved product. Section 505(b)(2) applications must include patent certifications described at 21 CFR 314.50(i) and must provide notice of certain patent certifications to the NDA holder and patent owner under 21 CFR 314.52.

VI. PATENT AND EXCLUSIVITY PROTECTIONS THAT COULD AFFECT A 505(B)(2) APPLICATION

A. What type of patent and/or exclusivity protection is a 505(b)(2) application eligible for?

A 505(b)(2) application may itself be granted 3 years of Waxman-Hatch exclusivity if one or more of the clinical investigations, other than BA/BE studies, was essential to approval of the application and was conducted or sponsored by the applicant (21 CFR 314.50(j); 314.108(b)(4) and (5)). A 505(b)(2) application may also be granted 5 years of exclusivity if it is for a new chemical entity (21 CFR 314.50(j); 314.108(b)(2)). A 505(b)(2) application may also be eligible for orphan drug exclusivity (21 CFR 314.20-316.36) or pediatric exclusivity (section 505A of the Act).

A 505(b)(2) application must contain information on patents claiming the drug or its method of use (21 CFR 314.54(a)(1)(v)).

B. What could delay the approval or filing of a 505(b)(2) application?

Approval or filing of a 505(b)(2) application, like a 505(j) application, may be delayed because of patent and exclusivity rights that apply to the listed drug (21 CFR 314.50(i), 314.107, and 314.108 and section 505A of the Act). This is the case even if the application also includes clinical investigations supporting approval of the application.

VII. WHAT SHOULD BE INCLUDED IN 505(B)(2) APPLICATIONS?

The Act (sections 505(b)(1) and (b)(2)) and FDA regulations (21 CFR 314.54) distinguish between 505(b)(1) and (b)(2) applications. Although the two types of applications must meet the same standards for approval (see section 505(b) and (c) of the Act), they differ in source of information to support safety and effectiveness, the patent certification requirements, BA/BE evidence, exclusivity bars, and processing within the FDA. The requirements for 505(b)(1) and 505(b)(2) applications are described at 21 CFR 314.50. Additional requirements for certain 505(b)(2) applications are described at 21 CFR 314.54.

A 505(b)(2) application should include the following:

- Identification of those portions of the application that rely on information the applicant does not own or to which the applicant does not have a right of reference (for example, for reproductive toxicity studies).

- If the 505(b)(2) seeks to rely on the Agency's previous finding of safety or efficacy for a listed drug or drugs, identification of any and all listed drugs by established name, proprietary name (if

any), dosage form, strength, route of administration, name of the listed drug's sponsor, and the application number (21 CFR 314.54(a)(1)(iii)). Even if the 505(b)(2) application is based solely upon literature and does not rely expressly on an Agency finding of safety and effectiveness for a listed drug, the applicant must identify the listed drug(s) on which the studies were conducted, if there are any. If the 505(b)(2) application is for an NCE and the 505(b)(2) applicant is not relying on literature derived from studies of an approved drug, there may not be a listed drug. If there is a listed drug that is the pharmaceutical equivalent to the drug proposed in the 505(b)(2) application, that drug should be identified as the listed drug.

- Information with respect to any patents that claim the drug or the use of the drug for which approval is sought (21 CFR 314.50(h)). This patent information will be published in the Orange Book when the application is approved.

- Information required under 314.50(j) if the applicant believes it is entitled to marketing exclusivity (21 CFR 314.54(a)(1)(vii)).

- A patent certification or statement as required under section 505(b)(2) of the Act with respect to any relevant patents that claim the listed drug and that claim any other drugs on which the investigations relied on by the applicant for approval of the application were conducted, or that claim a use for the listed or other drug (21 CFR 314.54(a)(1)(vi)).

  If there is a listed drug that is the pharmaceutical equivalent of the drug proposed in the 505(b)(2) application, the 505(b)(2) applicant should provide patent certifications for the patents listed for the pharmaceutically equivalent drug. Patent certifications should specify the exact patent number(s), and the exact name of the listed drug or other drug even if all relevant patents have expired.

- If an application is for approval of a new indication, and not for the indications approved for the listed drug, a certification so stating (21 CFR 314.54(a)(1)(iv).

- A statement as to whether the listed drug(s) identified above have received a period of marketing exclusivity (21 CFR 314.108(b)). If a listed drug is protected by exclusivity, filing or approval of the 505(b)(2) application may be delayed.

- A Bioavailability/Bioequivalence (BA/BE) study comparing the proposed product to the listed drug (if any).

- Studies necessary to support the change or modification from the listed drug or drugs (if any). Complete studies of safety and effectiveness may not be necessary if appropriate bridging studies are found to provide an adequate basis for reliance upon FDA's finding of safety and effectiveness of the listed drug(s).

Before submitting the application, the applicant should submit a plan to the appropriate new drug evaluation division identifying the types of bridging studies that should be conducted. The applicant should also identify those components of its application for which it expects to rely on FDA's finding of safety and effectiveness of a previously approved drug product. The division will critique the plan and provide guidance.

REFERENCES

April 10, 1987, letter from then Acting Director of the Center for Drugs and Biologics to all NDA and ANDA holders and applicants.

"Abbreviated New Drug Application Regulations; Proposed Rule," *Federal Register*. Vol. 54, No. 130, Monday, July 10, 1989, page 28872.

"Abbreviated New Drug Regulations; Final Rule," *Federal Register*. Vol. 57, No. 82, Tuesday, April 28, 1992, page 17950.

"Abbreviated New Drug Application Regulations; Patent and Exclusivity Provisions; Final Rule," *Federal Register*. Vol. 59, No. 190, Monday, October 3, 1994, page 50338.

GLOSSARY

505(b)(2) application: an application submitted under section 505(b)(1) of the Act for a drug for which one or more of the investigations relied on by the applicant for approval of the "application were not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted" (21 U.S.C. 355(b)(2)).

Active ingredient: "any component that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease, or to affect the structure or any function of the body of man or of animals. The term includes those components that may undergo chemical change in the manufacture of the drug product and be present in the drug product in a modified form intended to furnish the specified activity or effect" (21 CFR 60.3(b)(2)).

Active moiety: "the molecule or ion, excluding those appended portions of the molecule that cause the drug to be an ester, salt (including a salt with hydrogen or coordination bonds), or other noncovalent derivative (such as a complex, chelate, or clathrate) of the molecule, responsible for the physiological or pharmacological action of the drug substance" (21 CFR 314.108(a)).

Investigations relied on for approval: those without which the application cannot be approved (i.e., animal and human safety tests as well as clinical investigations of effectiveness).

Listed drug: "a new drug product that has an effective approval under section 505(c) of the act for safety and effectiveness or under section 505(j) of the act, which has not been withdrawn or suspended under section 505(e)(1) through (e)(5) or (j)(5) of the act, and which has not been withdrawn from sale for what FDA has determined are reasons of safety or effectiveness. Listed drug status is evidenced by the drug product's identification as a drug with an effective approval in the current edition of FDA's "Approved Drug Products with Therapeutic Equivalence Evaluations" (the list) or any current supplement thereto, as a drug with an effective approval. A drug product is deemed to be a listed drug on the date of effective approval of the application or abbreviated application for that drug product" (21 CFR 314.3(b)).

Literature: published reports of well-controlled studies that support safety or effectiveness; proposed and final monographs published in the *Federal Register*; the data supporting a *Federal Register* notice announcing a product's safety and/or effectiveness.

Orange Book: *Approved Drug Products with Therapeutic Equivalence Evaluations* and any current supplement to the publication.

Pharmaceutical equivalent or duplicate: "drug products that contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, in identical dosage forms, but not necessarily containing the same inactive ingredients, and that meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and,

where applicable, content uniformity disintegration times and/or dissolution rates" (21 CFR 320.1(c)). Products with different mechanisms of release can be considered to be pharmaceutical equivalents or duplicates.

Referenced listed drug: "the listed drug identified by FDA as the drug product upon which an applicant relies in seeking approval of its abbreviated application" (21 CFR 314.3(b)).

Right of reference or use: "the authority to rely upon, and otherwise use, an investigation for the purpose of obtaining approval of an application, including the ability to make available the underlying raw data from the investigation for FDA audit, if necessary" (21 CFR 314.3(b)).

Sponsors have the right of reference to any studies: (1) they conduct, (2) that are conducted for them, or (3) for which they formally obtain a documented *right of reference*.

An applicant is not considered to have a *right of reference* to published studies, because the applicant does not have access to the raw data. However, if the raw data are in the public domain, a right of reference is unnecessary.

Suitability petition: A citizen petition submitted to the Agency seeking permission to file an abbreviated new drug application for a change from a listed drug in dosage form, strength, route of administration, or active ingredient in a combination product. (See section 505(j)(2)(C) of the Act)