

## §314.1

### Subpart A—General Provisions

#### §314.1 Scope of this part.

(a) This part sets forth procedures and requirements for the submission to, and the review by, the Food and Drug Administration of applications and abbreviated applications to market a new drug under section 505 of the Federal Food, Drug, and Cosmetic Act, as well as amendments, supplements, and postmarketing reports to them.

(b) This part does not apply to drug products subject to licensing by FDA under the Public Health Service Act (58 Stat. 632 as amended (42 U.S.C. 201 *et seq.*)) and subchapter F of chapter I of title 21 of the Code of Federal Regulations.

(c) References in this part to regulations in the Code of Federal Regulations are to chapter I of title 21, unless otherwise noted.

[50 FR 7493, Feb. 22, 1985, as amended at 57 FR 17981, Apr. 28, 1992; 64 FR 401, Jan. 5, 1999]

#### §314.2 Purpose.

The purpose of this part is to establish an efficient and thorough drug review process in order to: (a) Facilitate the approval of drugs shown to be safe and effective; and (b) ensure the disapproval of drugs not shown to be safe and effective. These regulations are also intended to establish an effective system for FDA's surveillance of marketed drugs. These regulations shall be construed in light of these objectives.

#### §314.3 Definitions.

(a) The definitions and interpretations contained in section 201 of the Federal Food, Drug, and Cosmetic Act apply to those terms when used in this part and part 320 of this chapter.

(b) The following definitions of terms apply to this part and part 320 of this chapter:

*180-day exclusivity period* is the 180-day period beginning on the date of the first commercial marketing of the drug (including the commercial marketing of the reference listed drug) by any first applicant. The 180-day period ends on the day before the date on which an ANDA submitted by an applicant other than a first applicant could be approved.

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*505(b)(2) application* is an NDA submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for a drug for which at least some of the investigations described in section 505(b)(1)(A) of the Federal Food, Drug, and Cosmetic Act and relied upon by the applicant for approval of the NDA 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.

*Abbreviated application, abbreviated new drug application, or ANDA* is the application described under §314.94, including all amendments and supplements to the application.

*Acknowledgment letter* is a written, postmarked communication from FDA to an applicant stating that the Agency has determined that an ANDA is sufficiently complete to permit a substantive review. An acknowledgment letter indicates that the ANDA is regarded as received.

*Act* is the Federal Food, Drug, and Cosmetic Act (section 201 *et seq.* (21 U.S.C. 301 *et seq.*)).

*Active ingredient* is 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 other 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.

*Active moiety* is 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.

*ANDA holder* is the applicant that owns an approved ANDA.

*Applicant* is any person who submits an NDA (including a 505(b)(2) application) or ANDA or an amendment or supplement to an NDA or ANDA under this part to obtain FDA approval of a

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new drug and any person who owns an approved NDA (including a 505(b)(2) application) or ANDA.

*Application, new drug application, or NDA* is the application described under § 314.50, including all amendments and supplements to the application. An NDA refers to “stand-alone” applications submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act and to 505(b)(2) applications.

*Approval letter* is a written communication to an applicant from FDA approving an NDA or an ANDA.

*Assess the effects of the change* is to evaluate the effects of a manufacturing change on the identity, strength, quality, purity, and potency of a drug product as these factors may relate to the safety or effectiveness of the drug product.

*Authorized generic drug* is a listed drug, as defined in this section, that has been approved under section 505(c) of the Federal Food, Drug, and Cosmetic Act and is marketed, sold, or distributed directly or indirectly to the retail class of trade with labeling, packaging (other than repackaging as the listed drug in blister packs, unit doses, or similar packaging for use in institutions), product code, labeler code, trade name, or trademark that differs from that of the listed drug.

*Bioavailability* is the rate and extent to which the active ingredient or active moiety is absorbed from a drug product and becomes available at the site of drug action. For drug products that are not intended to be absorbed into the bloodstream, bioavailability may be assessed by scientifically valid measurements intended to reflect the rate and extent to which the active ingredient or active moiety becomes available at the site of drug action.

*Bioequivalence* is the absence of a significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study. Where there is an intentional difference in rate (e.g., in certain extended-release dosage forms), certain pharmaceutical equivalents or alter-

natives may be considered bioequivalent if there is no significant difference in the extent to which the active ingredient or moiety from each product becomes available at the site of drug action. This applies only if the difference in the rate at which the active ingredient or moiety becomes available at the site of drug action is intentional and is reflected in the proposed labeling, is not essential to the attainment of effective body drug concentrations on chronic use, and is considered medically insignificant for the drug. For drug products that are not intended to be absorbed into the bloodstream, bioequivalence may be assessed by scientifically valid measurements intended to reflect the rate and extent to which the active ingredient or active moiety becomes available at the site of drug action.

*Bioequivalence requirement* is a requirement imposed by FDA for in vitro and/or in vivo testing of specified drug products that must be satisfied as a condition of marketing.

*Class 1 resubmission* is the resubmission of an NDA or efficacy supplement, following receipt of a complete response letter, that contains one or more of the following: Final printed labeling, draft labeling, certain safety updates, stability updates to support provisional or final dating periods, commitments to perform post-marketing studies (including proposals for such studies), assay validation data, final release testing on the last lots used to support approval, minor reanalyses of previously submitted data, and other comparatively minor information.

*Class 2 resubmission* is the resubmission of an NDA or efficacy supplement, following receipt of a complete response letter, that includes any item not specified in the definition of “Class 1 resubmission,” including any item that would require presentation to an advisory committee.

*Commercial marketing* is the introduction or delivery for introduction into interstate commerce of a drug product described in an ANDA, outside the control of the ANDA applicant, except that the term does not include transfer of the drug product for investigational use under part 312 of this chapter or

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transfer of the drug product to parties identified in the ANDA for reasons other than sale. Commercial marketing includes the introduction or delivery for introduction into interstate commerce of the reference listed drug by the ANDA applicant.

*Complete response letter* is a written communication to an applicant from FDA usually describing all of the deficiencies that the Agency has identified in an NDA or ANDA that must be satisfactorily addressed before it can be approved.

*Component* is any ingredient intended for use in the manufacture of a drug product, including those that may not appear in such drug product.

*Date of approval* is the date on the approval letter from FDA stating that the NDA or ANDA is approved, except that the date of approval for an NDA described in section 505(x)(1) of the Federal Food, Drug, and Cosmetic Act is determined as described in section 505(x)(2) of the Federal Food, Drug, and Cosmetic Act. “Date of approval” refers only to a final approval and not to a tentative approval.

*Dosage form* is the physical manifestation containing the active and inactive ingredients that delivers a dose of the drug product. This includes such factors as:

- (1) The physical appearance of the drug product;
- (2) The physical form of the drug product prior to dispensing to the patient;
- (3) The way the product is administered; and
- (4) The design features that affect frequency of dosing.

*Drug product* is a finished dosage form, e.g., tablet, capsule, or solution, that contains a drug substance, generally, but not necessarily, in association with one or more other ingredients.

*Drug substance* is an active ingredient that is intended to furnish pharmaceutical 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 human body, but does not include intermediates used in the synthesis of such ingredient.

*Efficacy supplement* is a supplement to an approved NDA proposing to make one or more related changes from among the following changes to product labeling:

- (1) Add or modify an indication or claim;
- (2) Revise the dose or dose regimen;
- (3) Provide for a new route of administration;
- (4) Make a comparative efficacy claim naming another drug product;
- (5) Significantly alter the intended patient population;
- (6) Change the marketing status from prescription to over-the-counter use;
- (7) Provide for, or provide evidence of effectiveness necessary for, the traditional approval of a product originally approved under subpart H of this part; or
- (8) Incorporate other information based on at least one adequate and well-controlled clinical study.

*FDA or Agency* is the Food and Drug Administration.

*First applicant* is an ANDA applicant that, on the first day on which a substantially complete application containing a paragraph IV certification is submitted for approval of a drug, submits a substantially complete application that contains, and for which the applicant lawfully maintains, a paragraph IV certification for the drug.

*Inactive ingredient* is any component other than an active ingredient.

*Listed drug* is a new drug product that has been approved under section 505(c) of the Federal Food, Drug, and Cosmetic Act for safety and effectiveness or under section 505(j) of the Federal Food, Drug, and Cosmetic Act, which has not been withdrawn or suspended under section 505(e)(1) through (5) or section 505(j)(6) of the Federal Food, Drug, and Cosmetic 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 in the current edition of FDA's “Approved Drug Products With Therapeutic Equivalence Evaluations” (the list) as an approved drug. A drug product is deemed to be a listed drug on the date of approval for the NDA or ANDA for that drug product.

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*NDA holder* is the applicant that owns an approved NDA.

*Newly acquired information* is data, analyses, or other information not previously submitted to the Agency, which may include (but is not limited to) data derived from new clinical studies, reports of adverse events, or new analyses of previously submitted data (e.g., meta-analyses) if the studies, events, or analyses reveal risks of a different type or greater severity or frequency than previously included in submissions to FDA.

*Original application or original NDA* is a pending NDA for which FDA has never issued a complete response letter or approval letter, or an NDA that was submitted again after FDA had refused to file it or after it was withdrawn without being approved.

*Paragraph IV acknowledgment letter* is a written, postmarked communication from FDA to an applicant stating that the Agency has determined that a 505(b)(2) application or ANDA containing a paragraph IV certification is sufficiently complete to permit a substantive review. A paragraph IV acknowledgment letter indicates that the 505(b)(2) application is regarded as filed or the ANDA is regarded as received.

*Paragraph IV certification* is a patent certification of invalidity, unenforceability, or noninfringement described in § 314.50(i)(1)(i)(A)(4) or § 314.94(a)(12)(i)(A)(4).

*Patent owner* is the owner of the patent for which information is submitted for an NDA.

*Pharmaceutical alternatives* are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates.

*Pharmaceutical equivalents* are drug products in identical dosage forms and route(s) of administration that contain identical amounts of the identical active drug ingredient, *i.e.*, the same salt or ester of the same therapeutic moi-

ety, or, in the case of modified-release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; do not necessarily contain the same inactive ingredients; and 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.

*Postmark* is an independently verifiable evidentiary record of the date on which a document is transmitted, in an unmodifiable format, to another party. For postmarks made by the U.S. Postal Service or a designated delivery service, the date of transmission is the date on which the document is received by the domestic mail service of the U.S. Postal Service or by a designated delivery service. For postmarks documenting an electronic event, the date of transmission is the date (in a particular time zone) that FDA sends the electronic transmission on its host system as evidenced by a verifiable record. If the sender and the intended recipient are located in different time zones, it is the sender's time zone that provides the controlling date of electronic transmission.

*Reference listed drug* is the listed drug identified by FDA as the drug product upon which an applicant relies in seeking approval of its ANDA.

*Reference standard* is the drug product selected by FDA that an applicant seeking approval of an ANDA must use in conducting an *in vivo* bioequivalence study required for approval.

*Resubmission*, in the context of a complete response letter, is submission by the applicant of all materials needed to fully address all deficiencies identified in the complete response letter. An NDA or ANDA for which FDA issued a complete response letter, but which was withdrawn before approval and later submitted again, is not a resubmission.

*Right of reference or use* is the authority to rely upon, and otherwise use, an investigation for the purpose of obtaining approval of an NDA, including the

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ability to make available the underlying raw data from the investigation for FDA audit, if necessary.

*Same drug product formulation* is the formulation of the drug product submitted for approval and any formulations that have minor differences in composition or method of manufacture from the formulation submitted for approval, but are similar enough to be relevant to the Agency's determination of bioequivalence.

*Specification* is the quality standard (*i.e.*, tests, analytical procedures, and acceptance criteria) provided in an approved NDA or ANDA to confirm the quality of drug substances, drug products, intermediates, raw materials, reagents, components, in-process materials, container closure systems, and other materials used in the production of a drug substance or drug product. For the purpose of this definition, acceptance criteria means numerical limits, ranges, or other criteria for the tests described.

*Strength* is the amount of drug substance contained in, delivered, or deliverable from a drug product, which includes:

(1)(i) The total quantity of drug substance in mass or units of activity in a dosage unit or container closure (*e.g.*, weight/unit dose, weight/volume or weight/weight in a container closure, or units/volume or units/weight in a container closure); and/or, as applicable.

(ii) The concentration of the drug substance in mass or units of activity per unit volume or mass (*e.g.*, weight/weight, weight/volume, or units/volume); or

(2) Such other criteria the Agency establishes for determining the amount of drug substance contained in, delivered, or deliverable from a drug product if the weights and measures described in paragraph (i) of this definition do not apply (*e.g.*, certain drug-device combination products for which the amount of drug substance is emitted per use or unit time).

*Substantially complete application* is an ANDA that on its face is sufficiently complete to permit a substantive review. Sufficiently complete means that the ANDA contains all the information required under section 505(j)(2)(A) of

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the Federal Food, Drug, and Cosmetic Act and does not contain a deficiency described in §314.101(d) and (e).

*Tentative approval* is notification that an NDA or ANDA otherwise meets the requirements for approval under the Federal Food, Drug, and Cosmetic Act, but cannot be approved because there is a 7-year period of orphan exclusivity for a listed drug under section 527 of the Federal Food, Drug, and Cosmetic Act and §316.31 of this chapter, or that a 505(b)(2) application or ANDA otherwise meets the requirements for approval under the Federal Food, Drug, and Cosmetic Act, but cannot be approved until the conditions in §314.107(b)(1)(iii), (b)(3), or (c) are met; because there is a period of exclusivity for the listed drug under §314.108; because there is a period of pediatric exclusivity for the listed drug under section 505A of the Federal Food, Drug, and Cosmetic Act; because there is a period of exclusivity for the listed drug under section 505E of the Federal Food, Drug, and Cosmetic Act; or because a court order pursuant to 35 U.S.C. 271(e)(4)(A) orders that the NDA or ANDA may be approved no earlier than the date specified. A drug product that is granted tentative approval is not an approved drug and will not be approved until FDA issues an approval letter after any necessary additional review of the NDA or ANDA.

*The list* is the list of approved drug products published in FDA's current "Approved Drug Products With Therapeutic Equivalence Evaluations," available electronically on FDA's Web site at <http://www.fda.gov/cder>.

*Therapeutic equivalents* are approved drug products that are pharmaceutical equivalents for which bioequivalence has been demonstrated, and that can be expected to have the same clinical effect and safety profile when administered to patients under the conditions specified in the labeling.

[81 FR 69636, Oct. 6, 2016]

### Subpart B—Applications

#### §314.50 Content and format of an NDA.

NDAs and supplements to approved NDAs are required to be submitted in the form and contain the information,