SECTION-BY-SECTION REDLINE OF FDA'S FINAL REGULATIONS ON ANDAS AND 505(b)(2) APPLICATIONS TO IMPLEMENT TITLE XI OF THE MMA

21 C.F.R. § 314.3 – DEFINITIONS

(a) The definitions and interpretations contained in section 201 of the ~~act~~ 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.

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 ~~means~~ the application described under § 314.94, including all amendments and supplements to the application. ~~"Abbreviated application" applies to both an abbreviated new drug application and an abbreviated antibiotic application.~~

Acknowledgement 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 ~~means~~ the Federal Food, Drug, and Cosmetic Act (sections 201 *et seq.* ~~901~~ (21 U.S.C. 301 *et seq.* ~~392~~)).

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 ~~means~~ any person who submits an ~~application~~ NDA (including a 505(b)(2) application) or ~~abbreviated application~~ANDA or an amendment or supplement to ~~them~~ and~~d~~ NDA or ANDA under this part to obtain FDA approval of a new drug ~~or an antibiotic drug~~ and any person who owns an approved ~~application~~ NDA (including a 505(b)(2) application) or ~~abbreviated application~~ANDA.

Application, new drug application, or NDA is ~~means~~ 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.

~~*505(b)(2) Application* means an application submitted under section 505(b)(1) of the act for a drug for which the investigations described in section 505(b)(1)(A) of the act and relied upon 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.~~

Approval letter ~~means~~ is a written communication to an applicant from FDA approving an ~~application~~ NDA or an ~~abbreviated application~~ANDA.

Assess the effects of the change ~~means~~ 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 ~~means~~ is a listed drug, as defined in this section, that has been approved under section 505(c) of the ~~act~~ Federal Food, Drug, and Cosmetic Act and is marketed, sold, or distributed directly or indirectly to 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 alternatives 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 ~~means~~ is the resubmission of an ~~application~~ 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 postmarketing 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 ~~means~~ is the resubmission of an ~~application~~ 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 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 ~~means~~ is a written communication to an applicant from FDA usually describing all of the deficiencies that the ~~agency~~ Agency has identified in an ~~application~~ NDA or ~~abbreviated application~~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 ~~means~~ is a finished dosage form, ~~for example~~ 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 ~~means~~ is an active ingredient 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 human body, but does not include intermediates used in the synthesis of such ingredient.

Efficacy supplement ~~means~~ is a supplement to an approved ~~application~~ 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 part 314; or

(8) Incorporate other information based on at least one adequate and well-controlled clinical study.

~~*FDA*~~*FDA or Agency* ~~means~~ 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 ~~means~~ is a new drug product that has an effective approval under section 505(c) of the ~~act~~ Federal Food, Drug, and Cosmetic Act for safety and effectiveness or under section 505(j) of the ~~act~~Federal Food, Drug, and Cosmetic Act, which has not been withdrawn or suspended under section 505(e)(1) through ~~(e)~~(5) or section 505(j)(~~5~~6) of the ~~act~~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 ~~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 an approved drug ~~with an effective approval~~. A drug product is deemed to be a listed drug on the date of ~~effective~~ approval ~~of~~ for the ~~application~~ NDA or ~~abbreviated application~~ANDA for that drug product.

NDA holder is the applicant that owns an approved NDA.

Newly acquired information ~~means~~ is data, analyses, or other information not previously submitted to the ~~agency~~Agency, which may include (but ~~are~~ 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 ~~means~~ is a pending ~~application~~ NDA for which FDA has never issued a complete response letter or approval letter, or an ~~application~~ NDA that was submitted again after FDA had refused to file it or after it was withdrawn without being approved.

Paragraph IV acknowledgement 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 moiety, 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 ~~means~~ is the listed drug identified by FDA as the drug product upon which an applicant relies in seeking approval of its ~~abbreviated application~~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, ~~means~~ is submission by the applicant of all materials needed to fully address all deficiencies identified in the complete response letter. An ~~application~~ NDA or ~~abbreviated application~~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 ~~means~~ is the authority to rely upon, and otherwise use, an investigation for the purpose of obtaining approval of an ~~application~~NDA, including the 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 ~~means~~ is the quality standard (*i.e.*, tests, analytical procedures, and acceptance criteria) provided in an approved ~~application~~ 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 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 ~~means~~ is the list of drug products ~~with effective approvals~~ published in ~~the~~ FDA's current ~~edition of FDA's publication~~ "Approved Drug Products with Therapeutic Equivalence Evaluations," available electronically on FDA's Web site at http://www.fda.gov/cder. ~~and any current supplement to the publication.~~

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.

21 C.F.R. § 314.50 – CONTENT AND FORMAT OF AN ~~APPLICATION~~NDA

~~Applications~~ NDAs and supplements to approved ~~applications~~ NDAs are required to be submitted in the form and contain the information, as appropriate for the particular submission, required under this section. Three copies of the ~~application~~ NDA are required: An archival copy, a review copy, and a field copy. An ~~application~~ NDA for a new chemical entity will generally contain an application form, an index, a summary, five or six technical sections, case report tabulations of patient data, case report forms, drug samples, and labeling, including, if applicable, any Medication

Guide required under part 208 of this chapter. Other ~~applications~~ NDAs will generally contain only some of those items, and information will be limited to that needed to support the particular submission. These include an ~~application~~ NDA of the type described in section 505(b)(2) of the ~~act~~Federal Food, Drug, and Cosmetic Act, an amendment, and a supplement. The ~~application~~ NDA is required to contain reports of all investigations of the drug product sponsored by the applicant, and all other information about the drug pertinent to an evaluation of the application that is received or otherwise obtained by the applicant from any source. FDA will maintain guidance documents on the format and content of ~~applications~~ NDAs to assist applicants in their preparation.

(a) *Application form.* The applicant ~~shall~~ must submit a completed and signed application form that contains the following:

(1) The name and address of the applicant; the date of the ~~application~~NDA; the ~~application~~ NDA number if previously issued (for example, if the ~~application~~ NDA is a resubmission, an amendment, or a supplement); the name of the drug product, including its established, proprietary, code, and chemical names; the dosage form and strength; the route of administration; the identification numbers of all ~~investigational new drug applications~~INDs (as defined in § 312.3(b) of this chapter) that are referenced in the application; the identification numbers of all drug master files and other applications under this part that are referenced in the ~~application~~NDA; and the drug product's proposed indications for use.

(2) A statement whether the submission is an original submission, a 505(b)(2) application, a resubmission, or a supplement to an application under § 314.70.

(3) A statement whether the applicant proposes to market the drug product as a prescription or an over-the-counter product.

(4) A check-list identifying what enclosures required under this section the applicant is submitting.

(5) The applicant, or the applicant's attorney, agent, or other authorized official ~~shall~~ must sign the ~~application~~NDA. If the person signing the ~~application~~ NDA does not reside or have a place of business within the United States, the ~~application~~ NDA is required to contain the name and address of, and be countersigned by, an attorney, agent, or other authorized official who resides or maintains a place of business within the United States.

(b) *Index.* The archival copy of the ~~application~~ NDA is required to contain a comprehensive index by volume number and page number to the summary under paragraph (c) of this section, the technical sections under paragraph (d) of this section, and the supporting information under paragraph (f) of this section.

(c) *Summary.* (1) An ~~application~~ NDA is required to contain a summary of the ~~application~~ NDA in enough detail that the

reader may gain a good general understanding of the data and information in the ~~application~~NDA, including an understanding of the quantitative aspects of the data. The summary is not required for supplements under § 314.70. Resubmissions of an ~~application~~ NDA should contain an updated summary, as appropriate. The summary should discuss all aspects of the ~~application~~NDA, and synthesize the information into a well-structured and unified document. The summary should be written at approximately the level of detail required for publication in, and meet the editorial standards generally applied by, refereed scientific and medical journals. In addition to the agency personnel reviewing the summary in the context of their review of the ~~application~~NDA, FDA may furnish the summary to FDA advisory committee members and agency officials whose duties require an understanding of the ~~application~~NDA. To the extent possible, data in the summary should be presented in tabular and graphic forms. FDA has prepared a guideline under § 10.90(b) that provides information about how to prepare a summary. The summary required under this paragraph may be used by FDA or the applicant to prepare the Summary Basis of Approval document for public disclosure (under § 314.430(e)(2)(ii)) when the ~~application~~ NDA is approved.

(2) The summary is required to contain the following information:

(i) The proposed text of the labeling, including, if applicable, any Medication Guide required under part 208 of this chapter, for the drug, with annotations to the information in the summary and technical sections of the ~~application~~ NDA that support the inclusion of each statement in the labeling, and, if the ~~application~~ NDA is for a prescription drug, statements describing the reasons for omitting a section or subsection of the labeling format in § 201.57 of this chapter.

(ii) A statement identifying the pharmacologic class of the drug and a discussion of the scientific rationale for the drug, its intended use, and the potential clinical benefits of the drug product.

(iii) A brief description of the marketing history, if any, of the drug outside the United States, including a list of the countries in which the drug has been marketed, a list of any countries in which the drug has been withdrawn from marketing for any reason related to safety or effectiveness, and a list of countries in which applications for marketing are pending. The description is required to describe both marketing by the applicant and, if known, the marketing history of other persons.

(iv) A summary of the chemistry, manufacturing, and controls section of the ~~application~~NDA.

(v) A summary of the nonclinical pharmacology and toxicology section of the ~~application~~NDA.

(vi) A summary of the human pharmacokinetics and bioavailability section of the ~~application~~NDA.

(vii) A summary of the microbiology section of the ~~application~~ NDA (for anti-infective drugs only).

(viii) A summary of the clinical data section of the ~~application~~NDA, including the results of statistical analyses of the clinical trials.

(ix) A concluding discussion that presents the benefit and risk considerations related to the drug, including a discussion of any proposed additional studies or surveillance the applicant intends to conduct postmarketing.

(d) *Technical sections.* The ~~application~~ NDA is required to contain the technical sections described below. Each technical section is required to contain data and information in sufficient detail to permit the agency to make a knowledgeable judgment about whether to approve the ~~application~~ NDA or whether grounds exist under section 505(d) of the ~~act~~ Federal Food, Drug, and Cosmetic Act to refuse to approve the ~~application~~NDA. The required technical sections are as follows:

(1) *Chemistry, manufacturing, and controls section.* A section describing the composition, manufacture, and specification of the drug substance and the drug product, including the following:

(i) *Drug substance.* A full description of the drug substance including its physical and chemical characteristics and stability; the name and address of its manufacturer; the method of synthesis (or isolation) and purification of the drug substance; the process controls used during manufacture and packaging; and the specifications necessary to ensure the identity, strength, quality, and purity of the drug substance and the bioavailability of the drug products made from the substance, including, for example, tests, analytical procedures, and acceptance criteria relating to stability, sterility, particle size, and crystalline form. The ~~application~~ NDA may provide additionally for the use of alternatives to meet any of these requirements, including alternative sources, process controls, and analytical procedures. Reference to the current edition of the U.S. Pharmacopeia and the National Formulary may satisfy relevant requirements in this paragraph.

(ii)(a) *Drug product.* A list of all components used in the manufacture of the drug product (regardless of whether they appear in the drug product) and a statement of the composition of the drug product; the specifications for each component; the name and address of each manufacturer of the drug product; a description of the manufacturing and packaging procedures and in-process controls for the drug product; the specifications necessary to ensure the identity, strength, quality, purity, potency, and bioavailability of the drug product, including, for example, tests, analytical procedures, and acceptance criteria relating to sterility, dissolution rate, container

closure systems; and stability data with proposed expiration dating. The ~~application~~ NDA may provide additionally for the use of alternatives to meet any of these requirements, including alternative components, manufacturing and packaging procedures, in-process controls, and analytical procedures. Reference to the current edition of the U.S. Pharmacopeia and the National Formulary may satisfy relevant requirements in this paragraph.

(*b*) Unless provided by paragraph (d)(1)(ii)(*a*) of this section, for each batch of the drug product used to conduct a bioavailability or bioequivalence study described in § 320.38 or § 320.63 of this chapter or used to conduct a primary stability study: The batch production record; the specification for each component and for the drug product; the names and addresses of the sources of the active and noncompendial inactive components and of the container and closure system for the drug product; the name and address of each contract facility involved in the manufacture, processing, packaging, or testing of the drug product and identification of the operation performed by each contract facility; and the results of any test performed on the components used in the manufacture of the drug product as required by § 211.84(d) of this chapter and on the drug product as required by § 211.165 of this chapter.

(*c*) The proposed or actual master production record, including a description of the equipment, to be used for the manufacture of a commercial lot of the drug product or a comparably detailed description of the production process for a representative batch of the drug product.

(iii) *Environmental impact.* The ~~application~~ NDA is required to contain either a claim for categorical exclusion under § 25.30 or 25.31 of this chapter or an environmental assessment under § 25.40 of this chapter.

(iv) The applicant may, at its option, submit a complete chemistry, manufacturing, and controls section 90 to 120 days before the anticipated submission of the remainder of the ~~application~~NDA. FDA will review such early submissions as resources permit.

(v) The applicant ~~shall~~ must include a statement certifying that the field copy of the ~~application~~ NDA has been provided to the applicant's home FDA district office.

(2) *Nonclinical pharmacology and toxicology section.* A section describing, with the aid of graphs and tables, animal and in vitro studies with drug, including the following:

(i) Studies of the pharmacological actions of the drug in relation to its proposed therapeutic indication and studies that otherwise define the pharmacologic properties of the drug or are pertinent to possible adverse effects.

(ii) Studies of the toxicological effects of the drug as they relate to the drug's intended clinical uses, including, as appropriate,

studies assessing the drug's acute, subacute, and chronic toxicity; carcinogenicity; and studies of toxicities related to the drug's particular mode of administration or conditions of use.

(iii) Studies, as appropriate, of the effects of the drug on reproduction and on the developing fetus.

(iv) Any studies of the absorption, distribution, metabolism, and excretion of the drug in animals.

(v) For each nonclinical laboratory study subject to the good laboratory practice regulations under part 58 a statement that it was conducted in compliance with the good laboratory practice regulations in part 58, or, if the study was not conducted in compliance with those regulations, a brief statement of the reason for the noncompliance.

(3) *Human pharmacokinetics and bioavailability section.* A section describing the human pharmacokinetic data and human bioavailability data, or information supporting a waiver of the submission of in vivo bioavailability data under subpart B of part 320, including the following:

(i) A description of each of the bioavailability and pharmacokinetic studies of the drug in humans performed by or on behalf of the applicant that includes a description of the analytical procedures and statistical methods used in each study and a statement with respect to each study that it either was conducted in compliance with the institutional review board regulations in part 56, or was not subject to the regulations under § 56.104 or § 56.105, and that it was conducted in compliance with the informed consent regulations in part 50.

(ii) If the ~~application~~ NDA describes in the chemistry, manufacturing, and controls section tests, analytical procedures, and acceptance criteria needed to assure the bioavailability of the drug product or drug substance, or both, a statement in this section of the rationale for establishing the tests, analytical procedures, and acceptance criteria, including data and information supporting the rationale.

(iii) A summarizing discussion and analysis of the pharmacokinetics and metabolism of the active ingredients and the bioavailability or bioequivalence, or both, of the drug product.

(4) *Microbiology section.* If the drug is an anti-infective drug, a section describing the microbiology data, including the following:

(i) A description of the biochemical basis of the drug's action on microbial physiology.

(ii) A description of the antimicrobial spectra of the drug, including results of in vitro preclinical studies to demonstrate concentrations of the drug required for effective use.

(iii) A description of any known mechanisms of resistance to the drug,

including results of any known epidemiologic studies to demonstrate prevalence of resistance factors.

(iv) A description of clinical microbiology laboratory procedures (for example, in vitro sensitivity discs) needed for effective use of the drug.

(5) *Clinical data section.* A section describing the clinical investigations of the drug, including the following:

(i) A description and analysis of each clinical pharmacology study of the drug, including a brief comparison of the results of the human studies with the animal pharmacology and toxicology data.

(ii) A description and analysis of each controlled clinical study pertinent to a proposed use of the drug, including the protocol and a description of the statistical analyses used to evaluate the study. If the study report is an interim analysis, this is to be noted and a projected completion date provided. Controlled clinical studies that have not been analyzed in detail for any reason (e.g., because they have been discontinued or are incomplete) are to be included in this section, including a copy of the protocol and a brief description of the results and status of the study.

(iii) A description of each uncontrolled clinical study, a summary of the results, and a brief statement explaining why the study is classified as uncontrolled.

(iv) A description and analysis of any other data or information relevant to an evaluation of the safety and effectiveness of the drug product obtained or otherwise received by the applicant from any source, foreign or domestic, including information derived from clinical investigations, including controlled and uncontrolled studies of uses of the drug other than those proposed in the ~~application~~NDA, commercial marketing experience, reports in the scientific literature, and unpublished scientific papers.

(v) An integrated summary of the data demonstrating substantial evidence of effectiveness for the claimed indications. Evidence is also required to support the dosage and administration section of the labeling, including support for the dosage and dose interval recommended. The effectiveness data ~~shall~~ must be presented by gender, age, and racial subgroups and ~~shall~~ must identify any modifications of dose or dose interval needed for specific subgroups. Effectiveness data from other subgroups of the population of patients treated, when appropriate, such as patients with renal failure or patients with different levels of severity of the disease, also ~~shall~~ must be presented.

(vi) A summary and updates of safety information, as follows:

(*a*) The applicant ~~shall~~ must submit an integrated summary of all available information about the safety of the drug product, including pertinent animal data, demonstrated or potential adverse effects of

the drug, clinically significant drug/drug interactions, and other safety considerations, such as data from epidemiological studies of related drugs. The safety data ~~shall~~ must be presented by gender, age, and racial subgroups. When appropriate, safety data from other subgroups of the population of patients treated also ~~shall~~ must be presented, such as for patients with renal failure or patients with different levels of severity of the disease. A description of any statistical analyses performed in analyzing safety data should also be included, unless already included under paragraph (d)(5)(ii) of this section.

(*b*) The applicant ~~shall~~must, under section 505(i) of the ~~act~~Federal Food, Drug, and Cosmetic Act, update periodically its pending ~~application~~ NDA with new safety information learned about the drug that may reasonably affect the statement of contraindications, warnings, precautions, and adverse reactions in the draft labeling and, if applicable, any Medication Guide required under part 208 of this chapter. These "safety update reports" ~~are required to~~must include the same kinds of information (from clinical studies, animal studies, and other sources) and ~~are required to~~must be submitted in the same format as the integrated summary in paragraph (d)(5)(vi)(*a*) of this section. In addition, the reports ~~are required to~~must include the case report forms for each patient who died during a clinical study or who did not complete the study because of an adverse event (unless this requirement is waived). The applicant ~~shall~~ must submit these reports (*1*) 4 months after the initial submission; (*2*) in a resubmission following receipt of a complete response letter; and (*3*) at other times as requested by FDA. ~~Prior to the submission of~~Before submitting the first such report, applicants are encouraged to consult with FDA regarding further details on its form and content.

(vii) If the drug has a potential for abuse, a description and analysis of studies or information related to abuse of the drug, including a proposal for scheduling under the Controlled Substances Act. A description of any studies related to overdosage is also required, including information on dialysis, antidotes, or other treatments, if known.

(viii) An integrated summary of the benefits and risks of the drug, including a discussion of why the benefits exceed the risks under the conditions stated in the labeling.

(ix) A statement with respect to each clinical study involving human subjects that it either was conducted in compliance with the institutional review board regulations in part 56, or was not subject to the regulations under § 56.104 or § 56.105, and that it was conducted in compliance with the informed consent regulations in part 50.

(x) If a sponsor has transferred any obligations for the conduct of any clinical study to a contract research organization, a statement containing the name and address of the contract research organization, identification of the clinical study, and a listing of the obligations transferred. If all

obligations governing the conduct of the study have been transferred, a general statement of this transfer—in lieu of a listing of the specific obligations transferred—may be submitted.

(xi) If original subject records were audited or reviewed by the sponsor in the course of monitoring any clinical study to verify the accuracy of the case reports submitted to the sponsor, a list identifying each clinical study so audited or reviewed.

(6) *Statistical section.* A section describing the statistical evaluation of clinical data, including the following:

(i) A copy of the information submitted under paragraph (d)(5)(ii) of this section concerning the description and analysis of each controlled clinical study, and the documentation and supporting statistical analyses used in evaluating the controlled clinical studies.

(ii) A copy of the information submitted under paragraph (d)(5)(vi)(*a*) of this section concerning a summary of information about the safety of the drug product, and the documentation and supporting statistical analyses used in evaluating the safety information.

(7) *Pediatric use section.* A section describing the investigation of the drug for use in pediatric populations, including an integrated summary of the information (the clinical pharmacology studies, controlled clinical studies, or uncontrolled clinical studies, or other data or information) that is relevant to the safety and effectiveness and benefits and risks of the drug in pediatric populations for the claimed indications, a reference to the full descriptions of such studies provided under paragraphs (d)(3) and (d)(5) of this section, and information required to be submitted under § 314.55.

(e) *Samples and labeling.* (1) Upon request from FDA, the applicant ~~shall~~ must submit the samples described below to the places identified in the ~~agency's~~ Agency's request. FDA will generally ask applicants to submit samples directly to two or more ~~agency~~ Agency laboratories that will perform all necessary tests on the samples and validate the applicant's analytical procedures.

(i) Four representative samples of the following, each sample in sufficient quantity to permit FDA to perform three times each test described in the ~~application~~ NDA to determine whether the drug substance and the drug product meet the specifications given in the ~~application~~NDA:

(*a*) The drug product proposed for marketing;

(*b*) The drug substance used in the drug product from which the samples of the drug product were taken; and

(*c*) Reference standards and blanks (except that reference standards recognized in an official compendium need not be submitted).

(ii) Samples of the finished market package, if requested by FDA.

(2) The applicant ~~shall~~ must submit the following in the archival copy of the ~~application~~NDA:

(i) Three copies of the analytical procedures and related descriptive information contained in the chemistry, manufacturing, and controls section under paragraph (d)(1) of this section for the drug substance and the drug product that are necessary for FDA's laboratories to perform all necessary tests on the samples and to validate the applicant's analytical procedures. The related descriptive information includes a description of each sample; the proposed regulatory specifications for the drug; a detailed description of the methods of analysis; supporting data for accuracy, specificity, precision and ruggedness; and complete results of the applicant's tests on each sample.

(ii) Copies of the label and all labeling for the drug product (including, if applicable, any Medication Guide required under part 208 of this chapter) for the drug product (4 copies of draft labeling or 12 copies of final printed labeling).

(f) *Case report forms and tabulations.* The archival copy of the ~~application~~ NDA is required to contain the following case report tabulations and case report forms:

(1) *Case report tabulations.* The ~~application~~ NDA is required to contain tabulations of the data from each adequate and well-controlled study under § 314.126 (Phase 2 and Phase 3 studies as described in §§ 312.21 (b) and (c) of this chapter), tabulations of the data from the earliest clinical pharmacology studies (Phase 1 studies as described in § 312.21(a) of this chapter), and tabulations of the safety data from other clinical studies. Routine submission of other patient data from uncontrolled studies is not required. The tabulations are required to include the data on each patient in each study, except that the applicant may delete those tabulations which the agency agrees, in advance, are not pertinent to a review of the drug's safety or effectiveness. Upon request, FDA will discuss with the applicant in a "pre-NDA" conference those tabulations that may be appropriate for such deletion. Barring unforeseen circumstances, tabulations agreed to be deleted at such a conference will not be requested during the conduct of FDA's review of the ~~application~~NDA. If such unforeseen circumstances do occur, any request for deleted tabulations will be made by the director of the FDA division responsible for reviewing the ~~application~~NDA, in accordance with paragraph (f)(3) of this section.

(2) *Case report forms.* The ~~application~~ NDA is required to contain copies of individual case report forms for each patient who died during a clinical study or who did not complete the study because of an adverse event, whether believed to be drug related or not, including patients receiving

reference drugs or placebo. This requirement may be waived by FDA for specific studies if the case report forms are unnecessary for a proper review of the study.

(3) *Additional data.* The applicant ~~shall~~ must submit to FDA additional case report forms and tabulations needed to conduct a proper review of the ~~application~~NDA, as requested by the director of the FDA division responsible for reviewing the ~~application~~NDA. The applicant's failure to submit information requested by FDA within 30 days after receipt of the request may result in the agency viewing any eventual submission as a major amendment under § 314.60 and extending the review period as necessary. If desired by the applicant, the FDA division director will verify in writing any request for additional data that was made orally.

(4) Applicants are invited to meet with FDA before submitting an ~~application~~ NDA to discuss the presentation and format of supporting information. If the applicant and FDA agree, the applicant may submit tabulations of patient data and case report forms in ~~a form other than hard copy, for example, on microfiche or computer tapes~~an alternate form.

(g) *Other.* The following general requirements apply to the submission of information within the summary under paragraph (c) of this section and within the technical sections under paragraph (d) of this section.

(1) The applicant ordinarily is not required to resubmit information previously submitted, but may incorporate the information by reference. A reference to information submitted previously is required to identify the file by name, reference number, volume, and page number in the agency's records where the information can be found. A reference to information submitted to the agency by a person other than the applicant is required to contain a written statement that authorizes the reference and that is signed by the person who submitted the information.

(2) The applicant ~~shall~~ must submit an accurate and complete English translation of each part of the ~~application~~ NDA that is not in English. The applicant ~~shall~~ must submit a copy of each original literature publication for which an English translation is submitted.

(3) If an applicant who submits an ~~new drug application~~NDA under section 505(b) of the ~~act~~ Federal Food, Drug, and Cosmetic Act obtains a "right of reference or use," as defined under § 314.3(b), to an investigation described in clause (A) of section 505(b)(1) of the ~~act~~Federal Food, Drug, and Cosmetic Act, the applicant ~~shall~~ must include in its ~~application~~ NDA a written statement signed by the owner of the data from each such investigation that the applicant may rely on in support of the approval of its ~~application~~NDA, and provide FDA access to, the underlying raw data that provide the basis for the report of the investigation submitted in its ~~application~~NDA.

(h) *Patent information.* The ~~application~~ NDA is required to contain the patent information described under § 314.53.

(i) *Patent certification*—(1) *Contents.* A 505(b)(2) application is required to contain the following:

(i) *Patents claiming drug substance, drug product, or method of use.* (A) ~~Except as provided in paragraph (i)(2) of this section, a~~An appropriate patent certification with respect to each patent issued by the United States Patent and Trademark Office that, in the opinion of the applicant and to the best of its knowledge, claims ~~a~~ the drug ~~(the drug product or drug substance that is a component of the drug product)~~substance or drug product on which investigations that are relied upon by the applicant for approval of its 505(b)(2) application were conducted or that claims an approved use for such drug and for which information is required to be filed under section 505(b) and (c) of the ~~act~~ Federal Food, Drug, and Cosmetic Act and § 314.53. For each such patent, the applicant ~~shall~~ must provide the patent number and certify, in its opinion and to the best of its knowledge, one of the following circumstances:

(*1*) That the patent information has not been submitted to FDA. The applicant ~~shall~~ must entitle such a certification "Paragraph I Certification";

(*2*) That the patent has expired. The applicant ~~shall~~ must entitle such a certification "Paragraph II Certification";

(*3*) The date on which the patent will expire. The applicant ~~shall~~ must entitle such a certification "Paragraph III Certification"; or

(*4*)(*i*) That the patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the 505(b)(2) application is submitted. The applicant ~~shall~~ must entitle such a certification "Paragraph IV Certification". This certification shall be submitted in the following form:

~~I, (*NAME OF APPLICANT*), CERTIFY THAT PATENT NO. _____ (*IS INVALID, UNENFORCEABLE, OR WILL NOT BE INFRINGED BY THE MANUFACTURE, USE, OR SALE OF*) (*NAME OF PROPOSED DRUG PRODUCT*) FOR WHICH THIS APPLICATION IS SUBMITTED.~~I, (*name of applicant*), certify that Patent No. _____ (*is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of*) (*name of proposed drug product*) for which this 505(b)(2) application is submitted.

(*ii*) The certification ~~shall~~ must be accompanied by a statement that the applicant will comply with the requirements under § 314.52(a) with respect to providing a notice to each owner of the patent or ~~their~~ its representative~~s~~ and to the NDA holder ~~of the approved application~~ (or, if the NDA holder does not reside or maintain a place of business within the United States, its attorney, agent, or other authorized official) for the drug product ~~which~~ that is claimed by the patent or a use of which is claimed by

the patent and with the requirements under § 314.52(c) with respect to sending the notice and under § 314.52(c) with respect to the content of the notice.

(B) If the drug on which investigations that are relied upon by the applicant were conducted is itself a licensed generic drug of a patented drug first approved under section 505(b) of the ~~act~~Federal Food, Drug, and Cosmetic Act, ~~the~~ an appropriate patent certification or statement under this section with respect to each patent that claims the first-approved patented drug or that claims an approved use for such a drug.

(C) If, before the date of submission of an original 505(b)(2) application, there is a drug product approved in an NDA that is pharmaceutically equivalent to the drug product for which the original 505(b)(2) application is submitted, an appropriate patent certification or statement under this section with respect to each patent that claims the drug substance or drug product or that claims an approved use for one such drug product.

(ii) *No relevant patents.* If, in the opinion of the applicant and to the best of its knowledge, there are no patents described in paragraph (i)(1)(i) of this section, a certification in the following form:

~~IN THE OPINION AND TO THE BEST KNOWLEDGE OF (*NAME OF APPLICANT*), THERE ARE NO PATENTS THAT CLAIM THE DRUG OR DRUGS ON WHICH INVESTIGATIONS THAT ARE RELIED UPON IN THIS APPLICATION WERE CONDUCTED OR THAT CLAIM A USE OF SUCH DRUG OR DRUGS.~~In the opinion and to the best knowledge of (*name of applicant*), there are no patents that claim the drug or drugs on which investigations that are relied upon in this 505(b)(2) application were conducted or that claim a use of such drug or drugs.

(iii) *Method of use patent.* (A) If information that is submitted under section 505(b) or (c) of the ~~act~~ Federal Food, Drug, and Cosmetic Act and § 314.53 is for a ~~method of use~~method-of-use patent, and the labeling for the drug product for which the applicant is seeking approval does not include an~~y~~ indication~~s~~ or other condition of use that ~~are~~ is covered by the method-of-use patent, a statement explaining that the ~~method of use~~method-of-use patent does not claim a~~ny of the~~ proposed indication~~s~~ or other condition of use.

(B) If the labeling of the drug product for which the applicant is seeking approval includes an indication that, according to the patent information submitted under section 505(b) or (c) of the ~~act~~ Federal Food, Drug, and Cosmetic Act and § 314.53 or in the opinion of the applicant, is claimed by a method-of-use patent, the applicant ~~shall~~ must submit an applicable certification under paragraph (i)(1)(i) of this section.

(2) ~~*Method of manufacturing patent.* An applicant is not required to make a certification with respect to any patent that claims only a method of manufacturing the drug product for which the applicant is seeking approval.~~[Reserved]

(3) *Licensing agreements.* If a 505(b)(2) application is submitted for a drug or method of using a drug claimed by a patent and the applicant has a licensing agreement with the patent owner, the applicant ~~shall~~ must submit a paragraph IV certification ~~under paragraph (i)(1)(i)(A)(*4*) of this section ("Paragraph IV Certification")~~ as to that patent and a statement that ~~it~~ the applicant has been granted a patent license. If the patent owner consents to ~~an immediate effective date upon~~ approval of the 505(b)(2) application (if otherwise eligible for approval) as of a specific date, the 505(b)(2) application ~~shall~~ must contain a written statement from the patent owner that it has a licensing agreement with the applicant and that it consents to ~~an immediate effective date~~approval of the 505(b)(2) application as of a specific date.

(4) ~~*Late submission*~~*Untimely filing of patent information.* (i) If a patent described in paragraph (i)(1)(i)(A) of this section is issued and the holder of the approved ~~application~~ NDA for the patented drug does not ~~submit~~ file with FDA the required information on the patent within 30 days of issuance of the patent, an applicant who submitted a 505(b)(2) application that, before the submission of the patent information, contained an appropriate patent certification or statement is not required to submit ~~an amended certification~~a patent certification or statement to address the patent or patent information that is late-listed with respect to the pending 505(B)(2) application. Except as provided in § 314.53(f)(1), an NDA holder's amendment to the description of the approved method(S) of use claimed by the patent will be considered untimely filing of patent information unless:

(A) The amendment to the description of the approved method(s) of use claimed by the patent is submitted within 30 days of patent issuance;

(B) The amendment to the description of the approved method(s) of use claimed by the patent is submitted within 30 days of approval of a corresponding change to product labeling; or

(C) The amendment to the description of the approved method(s) of use claimed by the patent is submitted within 30 days of a decision by the U.S. Patent and Trademark Office or by a Federal district court, the Court of Appeals for the Federal Circuit, or the U.S. Supreme Court that is specific to the patent and alters the construction of a method-of-use claim(s) of the patent, and the amendment contains a copy of the decision.

(ii) An applicant whose 505(b)(2) application is ~~filed~~ submitted after ~~a late submission~~the NDA holder's untimely filing of patent information or whose 505(b)(2) application was previously filed but did not contain an appropriate patent certification or statement at the time of the patent submission ~~shall~~ must submit a certification under paragraph (i)(1)(i) or (i)(1)(ii) of this section and/or a statement under paragraph (i)(1)(iii) of this section as to that patent.

(5) *Disputed patent information.* If an applicant disputes the accuracy or relevance of patent information submitted to FDA, the applicant may seek a confirmation of the correctness of the patent information in accordance with the procedures under § 314.53(f). Unless the patent information is withdrawn ~~or changed~~, the applicant must submit an appropriate certification or statement for each ~~relevant~~ listed patent.

(6) *Amended certifications.* A certification submitted under paragraphs (i)(1)(i) through (i)(1)(iii) of this section may be amended at any time before the ~~effective date of the~~ approval of the 505(b)(2) application. An applicant ~~shall~~ must submit an amended certification as an amendment to a pending 505(b)(2) application ~~or by letter to an approved application~~. If an applicant with a pending 505(b)(2) application voluntarily makes a patent certification for an untimely filed patent, the applicant may withdraw the patent certification for the untimely filed patent. Once an amendment ~~or letter for the~~is submitted to change ~~in~~ the certification ~~has been submitted~~, the 505(b)(2) application will no longer be considered to ~~be one~~ contain~~ing~~ the prior certification.

(i) *After finding of infringement.* An applicant who has submitted a paragraph IV certification ~~under paragraph (i)(1)(i)(A)(*4*) of this section~~ and is sued for patent infringement ~~within 45 days of the receipt of notice sent under § 314.52 shall amend the~~must submit an amendment to change its certification if a court enters a final ~~judgment~~ decision from which no appeal has been or can be taken, or signs and enters a settlement order or consent decree in the action that includes a ~~in the action is entered~~ finding that the patent ~~to be~~is infringed, unless the final ~~judgment~~ decision, settlement order, or consent decree also finds the patent to be invalid. In ~~the~~ its ~~amended certification~~amendment, the applicant ~~shall~~ must certify under paragraph (i)(1)(i)(A)(*3*) of this section that the patent will expire on a specific date or, with respect to a patent claiming a method of use, the applicant may instead provide a statement under paragraph (i)(1)(iii) of this section if the applicant amends its 505(b)(2) application such that the applicant is not longer seeking approval for a method of use claimed by the patent. Once an amendment for the change has been submitted, the 505(b)(2) application will no longer be considered to contain a paragraph IV certification to the patent. If a final decision finds the patent to be invalid and infringed, an amended certification is not required.

(ii) *After request to remove~~al of~~ a patent or patent information from the list.* If ~~a patent is removed from the list~~the list reflects that an NDA holder has requested that a patent or patent information be removed from the list and no ANDA applicant is eligible for 180-day exclusivity based on a paragraph IV certification to that patent, the patent or patent information will be removed and any applicant with a pending 505(b)(2) application (including a tentatively approved 505(b)(2) application with a delayed effective date) who has made a certification with respect to such patent ~~shall amend~~must submit an amendment to

withdraw its certification. ~~The applicant shall certify under paragraph (i)(1)(ii) of this section that no patents described in paragraph (i)(1)(i) of this section claim the drug or, if other relevant patents claim the drug, shall amend the certification to refer only to those relevant patents.~~ In the amendment, the applicant ~~shall~~ must state the reason for ~~the change in~~withdrawing the certification or statement (that the patent ~~is or~~ has been removed from the list). If the list reflects that an NDA holder has requested that a patent or patent information be removed from the list and one or more first applicants are eligible for 180-day exclusivity based on paragraph IV certification to that patent, the patent will remain listed until any 180-day exclusivity based on that patent has expired or has been extinguished. A 505(b)(2) applicant is not required to provide or maintain a certification to a patent or patent information that remains listed only for purposes of a first applicant's 180-day exclusivity for its ANDA. ~~A patent that is the subject of a lawsuit under § 314.107(c) shall not be removed from the list until FDA determines either that no delay in effective dates of approval is required under that section as a result of the lawsuit, that the patent has expired, or that any such period of delay in effective dates of approval is ended. An applicant shall submit an amended certification as an amendment to a pending application.~~ Once an amendment ~~for the change~~to withdraw the certification has been submitted, the 505(b)(2) application will no longer be considered to ~~be one~~ contain~~ing~~ a paragraph IV certification to the patent ~~under paragraph (i)(1)(i)(A)(4) of this section~~. If removal of a patent from the list results in there being no patents listed for the listed drug(s) identified in the 505(b)(2) application, the applicant must submit an amended certification reflecting that there are no listed patents.

(iii) *Other amendments.* (A) Except as provided in paragraphs (i)(4) and (i)(6)(iii)(B) of this section:~~,~~

(*1*) ~~an~~ An applicant ~~shall~~ must amend a submitted certification or statement if, at any time before the ~~effective date of the~~ approval of the 505(b)(2) application, the applicant learns that the submitted certification or statement is no longer accurate~~.~~; and

(*2*) An applicant must submit an appropriate patent certification or statement under paragraph (i)(1) of this section if, after submission of the 505(b)(2) application, a new patent is issued by the U.S. Patent and Trademark Office that, in the opinion of the applicant and to the best of its knowledge, claims a listed drug relied upon or that claims an approved use for such listed drug for which information is required to be filed under section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act and § 314.53.

(B) An applicant is not required to submit a supplement to ~~amend~~ change a submitted certification when information on an otherwise applicable patent is submitted after the ~~effective date of~~ approval ~~for~~of the 505(b)(2) application.

(j) *Claimed exclusivity.* A new drug product, upon approval, may be entitled to a period of marketing exclusivity under the provisions of § 314.108. If an applicant believes its drug product is entitled to a period of exclusivity, it ~~shall~~ must submit with the ~~new drug application~~NDA prior to approval the following information:

(1) A statement that the applicant is claiming exclusivity.

(2) A reference to the appropriate paragraph under § 314.108 that supports its claim.

(3) If the applicant claims exclusivity under § 314.108(b)(2), information to show that, to the best of its knowledge or belief, a drug has not previously been approved under section 505(b) of the ~~act~~ Federal Food, Drug, and Cosmetic Act containing any active moiety in the drug for which the applicant is seeking approval.

(4) If the applicant claims exclusivity under § 314.108(b)(4) or (b)(5), the following information to show that the ~~application~~ NDA contains "new clinical investigations" that are "essential to approval of the ~~application~~ NDA or supplement" and were "conducted or sponsored by the applicant:"

(i) "*New clinical investigations.*" A certification that to the best of the applicant's knowledge each of the clinical investigations included in the ~~application~~ NDA meets the definition of "new clinical investigation" set forth in § 314.108(a).

(ii) "*Essential to approval.*" A list of all published studies or publicly available reports of clinical investigations known to the applicant through a literature search that are relevant to the conditions for which the applicant is seeking approval, a certification that the applicant has thoroughly searched the scientific literature and, to the best of the applicant's knowledge, the list is complete and accurate and, in the applicant's opinion, such published studies or publicly available reports do not provide a sufficient basis for the approval of the conditions for which the applicant is seeking approval without reference to the new clinical investigation(s) in the ~~application~~NDA, and an explanation as to why the studies or reports are insufficient.

(iii) "*Conducted or sponsored by.*" If the applicant was the sponsor named in the Form FDA ~~-~~ 1571 for an ~~investigational new drug application (~~IND~~)~~ under which the new clinical investigation(s) that is essential to the approval of its ~~application~~ NDA was conducted, identification of the IND by number. If the applicant was not the sponsor of the IND under which the clinical investigation(s) was conducted, a certification that the applicant or its predecessor in interest provided substantial support for the clinical investigation(s) that is essential to the approval of its ~~application~~NDA, and information supporting the certification. To demonstrate "substantial support," an applicant must either provide a certified statement from a certified public accountant that the applicant provided 50 percent or more of the cost of

conducting the study or provide an explanation of why FDA should consider the applicant to have conducted or sponsored the study if the applicant's financial contribution to the study is less than 50 percent or the applicant did not sponsor the investigational new drug. A predecessor in interest is an entity, e.g., a corporation, that the applicant has taken over, merged with, or purchased, or from which the applicant has purchased all rights to the drug. Purchase of nonexclusive rights to a clinical investigation after it is completed is not sufficient to satisfy this definition.

(k) *Financial certification or disclosure statement.* The ~~application~~ NDA ~~shall~~ must contain a financial certification or disclosure statement or both as required by part 54 of this chapter.

(l) *Format of an original ~~application~~NDA*—(1) *Archival copy.* The applicant must submit a complete archival copy of the ~~application~~ NDA that contains the information required under paragraphs (a) through (f) of this section. FDA will maintain the archival copy during the review of the ~~application~~ NDA to permit individual reviewers to refer to information that is not contained in their particular technical sections of the ~~application~~NDA, to give other agency personnel access to the ~~application~~ NDA for official business, and to maintain in one place a complete copy of the ~~application~~NDA. Except as required by paragraph (l)(1)(i) of this section, applicants may submit the archival copy on paper or in electronic format provided that electronic submissions are made in accordance with part 11 of this chapter.

(i) *Labeling.* The content of labeling required under § 201.100(d)(3) of this chapter (commonly referred to as the package insert or professional labeling), including all text, tables, and figures, must be submitted to the agency in electronic format as described in paragraph (l)(5) of this section. This requirement is in addition to the requirements of paragraph (e)(2)(ii) of this section that copies of the formatted label and all labeling be submitted. Submissions under this paragraph must be made in accordance with part 11 of this chapter, except for the requirements of § 11.10(a), (c) through (h), and (k), and the corresponding requirements of § 11.30.

(ii) [Reserved]

(2) *Review copy.* The applicant must submit a review copy of the ~~application~~NDA. Each of the technical sections, described in paragraphs (d)(1) through ~~(d)~~(6) of this section, in the review copy is required to be separately bound with a copy of the application form required under paragraph (a) of this section and a copy of the summary required under paragraph (c) of this section.

(3) *Field copy.* The applicant must submit a field copy of the ~~application~~ NDA that contains the technical section described in paragraph (d)(1) of this section, a copy of the application form required under paragraph (a) of this section, a copy of the summary required under paragraph (c) of

this section, and a certification that the field copy is a true copy of the technical section described in paragraph (d)(1) of this section contained in the archival and review copies of the ~~application~~NDA.

(4) *Binding folders.* The applicant may obtain from FDA sufficient folders to bind the archival, the review, and the field copies of the ~~application~~NDA.

(5) *Electronic format submissions.* Electronic format submissions must be in a form that FDA can process, review, and archive. FDA will periodically issue guidance on how to provide the electronic submission (e.g., method of transmission, media, file formats, preparation and organization of files).

21 C.F.R. § 314.52 – NOTICE OF CERTIFICATION OF INVALIDITY, UNENFORCEABILITY, OR NONINFRINGEMENT OF A PATENT

(a) *Notice of certification.* For each patent ~~which~~ that claims the listed drug or drugs ~~on which investigations that are~~ relied upon ~~by the applicant for approval of its application were conducted or which~~or that claims a use for such listed drug or drugs and which the 505(b)(2) applicant ~~certifies under § 314.50(i)(1)(i)(A)(4) that a patent is invalid, unenforceable, or will not be infringed~~submits a paragraph IV certification, the applicant ~~shall~~ must send notice of such certification by registered or certified mail, return receipt requested, or by a designated delivery service, as defined in paragraph (g) of this section, to each of the following persons:

(1) Each owner of the patent that is the subject of the certification or the representative designated by the owner to receive the notice. The name and address of the patent owner or its representative may be obtained from the ~~United States~~U.S. Patent and Trademark Office; and

(2) The holder of the approved ~~application~~ NDA under section 505(b) of the ~~act~~ Federal Food, Drug, and Cosmetic Act for each drug product which is claimed by the patent or a use of which is claimed by the patent and for which the applicant is seeking approval, or, if the ~~application~~ NDA holder does not reside or maintain a place of business within the United States, the ~~application~~ NDA holder's attorney, agent, or other authorized official. The name and address of the ~~application~~ NDA holder or its attorney, agent, or authorized official may be obtained by sending a written or electronic communication to~~from~~ the Orange Book Staff, Office of Generic Drugs, 7500 Standish Pl., Rockville, MD 20855, or to the Orange Book Staff at the email address listed on the Agency's Web site at http://www.fda.gov.

(3) This paragraph (a) does not apply to a method-of-use patent that does not claim~~s~~

~~no~~ a use~~s~~ for which the applicant is seeking approval.

(4) An applicant may send notice by an alternative method only if FDA has agreed in advance that the method will produce an acceptable form of documentation.

(b) *Sending the notice.* (1) Except as provided under paragraph (d) of this section, ~~The~~ the applicant ~~shall~~ must send the notice required by paragraph (a) of this section on or after the date of filing described in § ~~2~~314.101(a)(2) or (3), as applicable, but not later than 20 days after the date of the postmark on the paragraph IV acknowledgement letter. The 20-day clock described in this paragraph (B) begins on the day after the date of the postmark on the paragraph IV acknowledgement letter. When the 20th day falls on Saturday, Sunday, or a Federal holiday, the 20th day will be the next day that is not a Saturday, Sunday, or Federal holiday.~~when it receives from FDA an acknowledgment letter stating that its application has been filed.~~

(2) Any notice required by paragraph (a) of this section is invalid if it is sent before the date of filing described in § 314.101(a)(2) or, if FDA notifies the applicant that FDA has refused to file the 505(b)(2) application, before the date described in § 314.101(a)(3) on which the 505(b)(2) application is filed. The applicant will not have complied with this paragraph (b) until it sends valid notice.

(3) ~~At the same time, t~~The applicant ~~shall amend its~~must submit to FDA an amendment to its 505(b)(2) application ~~to~~ that includes a statement certifying that the notice has been provided to each person identified under paragraph (a) of this section and that the notice met the content requirement under paragraph (c) of this section. A copy of the notice itself need not be submitted to the Agency.

(c) *Content of a notice.* In the notice, the applicant shall cite section 505(b)(3)(~~B~~D) of the ~~act~~ Federal Food, Drug, and Cosmetic Act and the notice~~and shall~~ must include, but not be limited to, the following information:

(1) A statement that a 505(b)(2) application that contains any required bioavailability or bioequivalence studies has been submitted by the applicant and~~has been~~ filed by FDA.

(2) The ~~application~~ NDA number.

(3) The established name, if any, as defined in section 502(e)(3) of the ~~act~~Federal Food, Drug, and Cosmetic Act, of the proposed drug product.

(4) The active ingredient, strength, and dosage form of the proposed drug product.

(5) The patent number and expiration date~~, as submitted to the agency or as known to the applicant,~~ of each patent on the list alleged to be invalid, unenforceable, or not infringed.

(6) A detailed statement of the factual and legal basis of the applicant's opinion that

the patent is not valid, unenforceable, or will not be infringed. The applicant ~~shall~~ must include in the detailed statement:

(i) For each claim of a patent alleged not to be infringed, a full and detailed explanation of why the claim is not infringed.

(ii) For each claim of a patent alleged to be invalid or unenforceable, a full and detailed explanation of the grounds supporting the allegation.

(7) If the applicant alleges that the patent will not be infringed and the applicant seeks to preserve the option to later file a civil action for declaratory judgment in accordance with section 505(c)(3)(D) of the Federal Food, Drug, and Cosmetic Act, then the notice must be accompanied by an offer of confidential access to the 505(b)(2) application for the sole and limited purpose of evaluating possible infringement of the patent that is the subject of the paragraph IV certification.

(~~7~~8) If the applicant does not reside or have a place of business in the United States, the name and address of an agent in the United States authorized to accept service of process for the applicant.

(d) *Amendment to an application.* (1) If, after the date of filing described in § 314.101(a)(2) or (3), as applicable, an applicant submits an amendment or supplement to its 505(b)(2) application that includes a paragraph IV certification~~is amended to include the certification described in § 314.50(i)~~, the applicant ~~shall~~ must send the notice required by paragraph (a) of this section at the same time that the amendment or supplement to the 505(b)(2) application is submitted to ~~FDA~~FDA, regardless of whether the applicant has already given notice with respect to another such certification contained in the 505(b)(2) application or in an amendment or supplement to the 505(b)(2) application.

(2) If, before the date of filing described in § 314.101(a)(2) or (3), as applicable, an applicant submits a paragraph IV certification in an amendment, the applicant must send the notice required by paragraph (a) of this section in accordance with the procedures in paragraph (b) of this section.

(3) An applicant that submits an amendment or supplement to seek approval of a different strength must provide notice of any paragraph IV certification in accordance with paragraph (d)(1) or (2) of this section, as applicable.

(e) *Documentation of timely sending and receipt of notice.* The applicant ~~shall~~ must amend its 505(b)(2) application to provide documentation of the date of receipt of the notice required under paragraph (a) of this section by each person provided the notice. The amendment must be submitted to FDA within 30 days after the last date on which notice was received by a person described in paragraph (a) of this section. The applicant's amendment also ~~shall~~ must include documentation that its notice was sent on a date that complies with the timeframe required by paragraph (b) or (d) of this

section, as applicablea copy of the return receipt or other similar evidence of the date the notification was received. FDA will accept, as adequate documentation of the date the notice was sent, a copy of the registered mail receipt, certified mail receipt, or receipt from a designated delivery service, as defined in paragraph (g) of this section. FDA will accept as adequate documentation of the date of receipt a return receipt, a signature proof of delivery by a designated delivery service, or a letter acknowledging receipt by the person provided the notice. An applicant may rely on another form of documentation only if FDA has agreed to such documentation in advance. A copy of the notice itself need not be submitted to the agencyAgency.

(f) *ApprovalForty-five day period after receipt of notice*. If the requirements of this section are met, the agency Agency will presume the notice to be complete and sufficient, and it will count the day following the date of receipt of the notice by the patent owner or its representative and by the approved application NDA holder or its attorney, agent, or other authorized official as the first day of the 45-day period provided for in section 505(c)(3)(C) of the actFederal Food, Drug, and Cosmetic Act. FDA may, if the applicant amends its 505(b)(2) application with a written statement that a later date should be used, count from such later date.

(g) *Designated delivery services*. (1) For purposes of this section, the term "designated delivery service" is any delivery service provided by a trade or business that the Agency determines:

(i) Is available to the general public throughout the United States;

(ii) Records electronically to its database, kept in the regular course of its business, or marks on the cover in which any item referred to in this section is to be delivered, the date on which such item was given to such trade or business for delivery; and

(iii) Provides overnight or 2-day delivery service throughout the United States.

(2) FDA may periodically issue guidance regarding designated delivery services.

21 C.F.R. § 314.53 – SUBMISSION OF PATENT INFORMATION

(a) *Who must submit patent information.* This section applies to any applicant who submits to FDA an new drug applicationNDA or an amendment to it under section 505(b) of the act Federal Food, Drug, and Cosmetic Act and § 314.50 or a supplement to an approved application NDA under § 314.70, except as provided in paragraph (d)(2) of this section.

(b) *Patents for which information must be submitted and patents for which information must not be submitted—*
(1) *General requirements.* An applicant described in paragraph (a) of this section ~~shall~~ must submit to its NDA the required information, on the required FDA declaration form, set forth in paragraph (c) of this section for each patent that claims the drug or a method of using the drug that is the subject of the ~~new drug application~~NDA or amendment or supplement to it and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product. For purposes of this part, such patents consist of drug substance (active ingredient) patents, drug product (formulation and composition) patents, and method-of-use patents. For patents that claim the drug substance, the applicant ~~shall~~ must submit information only on those patents that claim the drug substance that is the subject of the pending or approved ~~application~~ NDA or that claim a drug substance that is the same as the active ingredient that is the subject of the approved or pending ~~application~~NDA. For patents that claim only a polymorph that is the same as the active ingredient described in the approved or pending ~~application~~NDA, the applicant ~~shall~~ must certify in the required FDA declaration form~~s~~ that the applicant has test data, as set forth in paragraph (b)(2) of this section, demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the ~~new drug application~~NDA. For patents that claim a drug product, the applicant shall submit information only on those patents that claim ~~a~~ the drug product, as is defined in § 314.3, that is described in the pending or approved ~~application~~NDA. For patents that claim a method of use, the applicant ~~shall~~ must submit information only on those patents that claim indications or other conditions of use ~~that are described in the pending or approved application~~for which approval is sought or has been granted in the NDA. The applicant ~~shall~~ must separately identify each pending or approved method of use and related patent claim(s). For approved ~~applications~~NDAs, the ~~applicant~~ NDA holder's description of the patented method of use required by paragraph (c)(2)(ii)(P)(3) of this section must describe only the approved method(s) of use claimed by the patent for which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product. If the method(s) of use claimed by the patent does not cover an indication or other approved condition of use in its entirety, the applicant must describe only the specific approved method of use claimed by the patent for which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engage in the manufacture, use, or sale of the drug product. For approved NDAs, the NDA holder submitting information on the method-of-use patent ~~shall~~ must identify with specificity the section(s) and subsection(s) of the approved labeling that ~~corresponds to~~describes the method(s) of use claimed by the patent submitted. Process patents, patents claiming

packaging, patents claiming metabolites, and patents claiming intermediates are not covered by this section, and information on these patents must not be submitted to FDA.

(2) *Test ~~Data~~ data for ~~Submission~~ submission of ~~Patent~~ patent ~~Information~~ information for ~~Patents~~ patents ~~That~~ that ~~Claim~~ claim only a ~~Polymorph~~polymorph*. The test data, referenced in paragraph (b)(1) of this section, must include the following:

(i) A full description of the polymorphic form of the drug substance, including its physical and chemical characteristics and stability; the method of synthesis (or isolation) and purification of the drug substance; the process controls used during manufacture and packaging; and such specifications and analytical methods as are necessary to assure the identity, strength, quality, and purity of the polymorphic form of the drug substance;

(ii) The executed batch record for a drug product containing the polymorphic form of the drug substance and documentation that the batch was manufactured under current good manufacturing practice requirements;

(iii) Demonstration of bioequivalence between the executed batch of the drug product that contains the polymorphic form of the drug substance and the drug product as described in the NDA;

(iv) A list of all components used in the manufacture of the drug product containing the polymorphic form and a statement of the composition of the drug product; a statement of the specifications and analytical methods for each component; a description of the manufacturing and packaging procedures and in-process controls for the drug product; such specifications and analytical methods as are necessary to assure the identity, strength, quality, purity, and bioavailability of the drug product, including release and stability data complying with the approved product specifications to demonstrate pharmaceutical equivalence and comparable product stability; and

(v) Comparative in vitro dissolution testing on 12 dosage units each of the executed test batch and the ~~new drug application~~NDA product.

(c) *Reporting requirements*—(1) *General requirements.* An applicant described in paragraph (a) of this section ~~shall~~ must submit the required patent information described in paragraph (c)(2) of this section for each patent that meets the requirements described in paragraph (b) of this section. We will not accept the patent information unless it is ~~complete and~~ submitted on the appropriate form~~s~~, Form FDA ~~Forms~~ 3542 or 3542a, and contains the information required in paragraph (c)(2) of this section. These forms may be obtained on the Internet at http://www.fda.gov by searching for "forms".

(2) *Drug substance (active ingredient), drug product (formulation or composition), and method-of-use patents*—(i) *Original ~~Declaration~~declaration*. For each patent that claims a drug substance (active ingredient),

drug product (formulation and composition), or method of use, the applicant ~~shall~~ must submit ~~FDA~~ Form FDA 3542a. The following information and verification is required, subject to the exceptions listed in paragraph (c)(2)(i)(S) of this section:

(A) ~~New drug application~~NDA number;

(B) ~~Name of new drug application sponsor~~The NDA applicant's name, full address, phone number and, if available, fax number and email address;

(C) Trade name (or proposed trade name) of new drug;

(D) Active ingredient(s) of new drug;

(E) Strength(s) of new drug;

(F) Dosage form(s) and route(s) of administration of new drug, and whether the applicant proposes to market the new drug for prescription use or over-the-counter use;

(G) ~~United States~~U.S. patent number, issue date, and expiration date of patent submitted;

(H) The patent owner's name, full address, phone number and, if available, fax number and e-mail address;

(I) The name, full address, phone number and, if available, fax number and e-mail address of an agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under sections 505(b)(3) and 505(j)(2)(B) of the ~~act~~ Federal Food, Drug, and Cosmetic Act and §§ 314.52 and 314.95 (if patent owner or ~~new drug application~~NDA applicant or holder does not reside or have a place of business within the United States);

(J) Information on whether the patent has been submitted previously for the ~~new drug application~~NDA or supplement;

(K) If the patent has been submitted previously for listing, identify all change(s) from the previously submitted patent information and specify whether the change is related to the patent or related to an FDA action or procedure;

~~(K) Information on whether the expiration date is a new expiration date if the patent had been submitted previously for listing;~~

(L) Information on whether the patent is a product-by-process patent in which the product claimed is novel;

(M) Information on the drug substance (active ingredient) patent, including the following:

(*1*) Whether the patent claims ~~the~~ a drug substance that is ~~the~~ an active ingredient in the drug product described in ~~the new drug application~~NDA or supplement;

(*2*) Whether the patent claims only a polymorph that is the same active ingredient that is described in the pending ~~application~~ NDA or supplement;

(*3*) Whether the applicant has test data, described in paragraph (b)(2) of this section, demonstrating that a drug product containing only the polymorph will perform the same as the drug product described in the ~~new drug application~~NDA or supplement, and a description of the polymorphic form(s) claimed by the patent for which such test data exist;

(*4*) Whether the patent claims only a metabolite of the active ingredient; and

(*5*) Whether the patent claims only an intermediate;

(N) Information on the drug product (composition/formulation) patent, including the following:

(*1*) Whether the patent claims the drug product for which approval is being sought, as defined in § 314.3; and

(*2*) Whether the patent claims only an intermediate;

(O) Information on each method-of-use paten~~.~~t, including the following:

(*1*) Whether the patent claims one or more methods of using the drug product for which ~~use~~ approval is being sought and a description of each pending method of use ~~or related indication~~ and related patent claim of the patent being submitted; ~~and~~

(*2*) Identification of the specific section(s) of the proposed labeling for the drug product that describes~~corresponds to~~ the method of use claimed by the patent submitted; and

(*3*) An applicant that submits information for a patent that claims one or more methods of using the drug product must also submit information described in either paragraph (c)(2)(i)(M) or (N) of this section, regarding whether that patent also claims either the drug substance (active ingredient) or the drug product (composition/formulation).

(P) Whether there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition), or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product;

(Q) A signed verification ~~which~~ that states: "The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.";

(R) Information on whether the applicant, patent owner or attorney, agent, representative or other authorized official signed the form; the name of the person; and the full address, phone number and, if available, the fax number and e-mail address~~.~~; and

(S) Exceptions to required submission of patent information:

(*1*) If an applicant submits the information described in paragraph (c)(2)(i)(M) of this section for a patent that claims the drug substance (active ingredient) and meets the requirements for listing on that basis, then the applicant is not required to provide the information described in paragraph (c)(2)(i)(N) of this section on whether that patent also claims the drug product (composition/formulation);

(*2*) If an applicant submits the information described in paragraph (c)(2)(i)(N) of this section for a patent that claims the drug product (composition/formulation) and meets the requirements for listing on that basis, then the applicant is not required to provide the information described in paragraph (c)(2)(i)(M) of this section on whether that patent also claims the drug substance (active ingredient);

(*3*) If the applicant submits a supplement for a change other than one of the changes listed under paragraph (d)(2)(i) of this section, then the patent information submission requirements of paragraph (d)(2)(ii) of this section apply.

(ii) *Submission of patent information upon and after approval.* Within 30 days after the date of approval of its ~~application~~ NDA or supplement, the applicant ~~shall~~ must submit Form FDA ~~Form~~ 3542 for each patent that claims the drug substance (active ingredient), drug product (formulation and composition), or approved method of use. ~~FDA will rely only on the information submitted on this form and~~ FDA will not list or publish patent information if~~-~~ it is not provided on this form or if the patent declaration does not contain the required information ~~the patent declaration is incomplete~~ or indicates the patent is not eligible for listing. Patent information must also be submitted for patents issued after the date of approval of the ~~new drug application~~NDA as required in paragraph (c)(2)(ii) of this section. As described in paragraph (d)(3~~4~~) of this section, to be timely filed, patent information for patents issued after the date of approval of the NDA must be submitted to FDA within 30 days of the date of issuance of the patent. If the applicant submits the required patent information within the 30 days, but we notify an applicant that a declaration form is incomplete or shows that the patent is not eligible for listing, the applicant must submit an acceptable declaration form within 15 days of FDA notification to be considered timely filed. The following information and verification statement is required, subject to the exceptions listed in paragraph (c)(2)(ii)(T):

(A) ~~New drug application~~NDA number;

(B) ~~Name of new drug application sponsor~~The NDA holder's name, full address, phone number and, if available, fax number and email address~~.~~;

(C) Trade name of new drug;

(D) Active ingredient(s) of new drug;

(E) Strength(s) of new drug;

(F) Dosage form(s) and route(s) of administration of new drug, and whether the new drug is approved for prescription use or over-the-counter use;

(G) Approval date of ~~new drug application~~NDA or supplement;

(H) ~~United States~~U.S. patent number, issue date, and expiration date of patent submitted;

(I) The patent owner's name, full address, phone number and, if available, fax number and e-mail address;

(J) The name, full address, phone number and, if available, fax number and e-mail address of an agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under sections 505(b)(3) and ~~505~~(j)(2)(B) of the ~~act~~ Federal Food, Drug, and Cosmetic Act and §§ 314.52 and 314.95 (if patent owner or ~~new drug application~~NDA applicant or holder does not reside or have a place of business within the United States);

(K) Information on whether the patent has been submitted previously for the ~~new drug application~~NDA or supplement;

(L) ~~Information on whether the expiration date is a new expiration date if the patent had been submitted previously for listing~~If the patent has been submitted previously for listing, identify all change(s) from the previously submitted patent information and specify whether the change is related to the patent or related to an FDA action or procedure;

(M) Information on whether the patent is a product-by-process patent in which the product claimed is novel;

(N) Information on the drug substance (active ingredient) patent, including the following:

(*1*) Whether the patent claims ~~the~~ a drug substance that is an~~the~~ active ingredient in the drug product described in the approved NDA~~application~~;

(*2*) Whether the patent claims only a polymorph that is the same as the active ingredient that is described in the approved ~~application~~NDA;

(*3*) Whether the applicant has test data, described at paragraph (b)(2) of this section, demonstrating that a drug product containing only the polymorph will perform the same as the drug product described in the approved ~~application~~ NDA and a description of the polymorphic form(s)

claimed by the patent for which such test data exist;

(*4*) Whether the patent claims only a metabolite of the active ingredient; and

(*5*) Whether the patent claims only an intermediate;

(O) Information on the drug product (composition/formulation) patent, including the following:

(*1*) Whether the patent claims the approved drug product as defined in § 314.3; and

(*2*) Whether the patent claims only an intermediate;

(P) Information on each method-of-use patent including the following:

(*1*) Whether the patent claims one or more approved methods of using the approved drug product and a description of each approved method of use or indication and related patent claim of the patent being submitted;

(*2*) Identification of the specific section(s) and subsection(s) of the approved labeling for the drug product ~~that corresponds to~~ that describes the method of use claimed by the patent submitted; and

(*3*) The description of the patented method of use as required for publication, which must contain adequate information to assist 505(b)(2) and ANDA applicants in determining whether a listed method-of-use patent claims a use for which the 505(b)(2) or ANDA applicant is not seeking approval (for example, if the method(s) of use claimed by the patent does not cover an indication or other approved condition of use in its entirety, then the applicant must describe only the specific approved method of use claimed by the patent for which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product);

(*4*) An applicant that submits information for a patent that claims one or more methods of using the drug product must also submit information described in either paragraph (c)(2)(ii)(N) or (O) of this section, regarding whether that patent also claims either the drug substance (active ingredient) or the drug product (composition/formulation).

(Q) Whether there are no relevant patents that claim the approved drug substance (active ingredient), the approved drug product (formulation or composition) or approved method(s) of use and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product;

(R) A signed verification ~~which~~ that states: "The undersigned declares that this is an accurate and complete submission of patent information for the NDA,

amendment, or supplement approved under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information or response to a request under 21 CFR 314.53(f)(1) is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct."~~; and~~

(S) Information on whether the applicant, patent owner or attorney, agent, representative, or other authorized official signed the form; the name of the person; and the full address, phone number and, if available, the fax number and e-mail address.

(T) Exceptions to required submission of patent information:

(*1*) If an applicant submits the information described in paragraph (c)(2)(ii)(N) of this section for a patent that claims the drug substance (active ingredient) and meets the requirements for listing on that basis, then the applicant is not required to provide the information described in paragraph (c)(2)(ii)(O) of this section on whether that patent also claims the drug product (composition/formulation).

(*2*) If an applicant submits the information described in paragraph (c)(2)(ii)(O) of this section for a patent that claims the drug product (composition/formulation) and meets the requirements for listing on that basis, then the applicant is not required to provide the information described in paragraph (c)(2)(ii)(N) of this section on whether that patent also claims the drug substance (active ingredient).

(*3*) If the applicant submits a supplement for a change other than one of the changes listed under paragraph (d)(2)(i) of this section, then the patent information submission requirements of paragraph (d)(2)(ii) of this section apply

(3) *No relevant patents.* If the applicant believes that there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition), or the method(s) of use for which the applicant has received approval, and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product, the applicant will verify this information in the appropriate form~~s~~, ~~FDA~~ Form~~s~~ FDA 3542 or 3542a.

(4) *Authorized signature.* The declarations required by this section ~~shall~~ must be signed by the applicant or patent owner, or the applicant's or patent owner's attorney, agent (representative), or other authorized official.

(d) *When and where to submit patent information*—(1) *Original ~~application~~NDA*. An applicant ~~shall~~ must submit with its original ~~application~~ NDA submitted under this part, ~~including an application described in section 505(b)(2) of the act,~~ the information described in

paragraph (c) of this section on each drug substance (active ingredient), drug product (formulation and composition), and method of use patent issued before the ~~application~~ NDA is filed with FDA and for which patent information is required to be submitted under this section. If a patent is issued after the ~~application~~ NDA is filed with FDA but before the ~~application~~ NDA is approved, the applicant must~~shall~~, within 30 days of the date of issuance of the patent, submit the required patent information in an amendment to the ~~application~~ NDA under § 314.60.

(2) *Supplements.* (i) An applicant ~~shall~~ must submit patent information required under paragraph (c) of this section for a patent that claims the drug substance, drug product, or method of use for which approval is sought in any of the following supplements:

(A) To add or change the ~~formulation~~dosage form or route of administration;

(B) ~~To add a new indication or other condition of use, including a change in route of administration~~To add or change the strength; or

(C) To change the ~~strength~~drug product from prescription use to over-the-counter use.~~;~~

~~(D) To make any other patented change regarding the drug, drug product, or any method of use.~~

(ii) If the applicant submits a supplement for a change other than one of the changes listed under paragraph (d)(2)(i) of this section (for example, to change the formulation, to add a new indication or other condition of use, or to make any other patented change regarding the drug substance, drug product, or any method of use) ~~and existing patents for which information has already been submitted to FDA claim the changed product, the applicant shall submit a certification with the supplement identifying the patents that claim the changed product~~the following patent information submission requirements apply:~~.~~

(A) If existing patents for which information required by paragraph (c) of this section has already been submitted to FDA for the product approved in the original NDA claim the changed product, the applicant is not required to resubmit this patent information pursuant to paragraph (c) of this section unless the published description of the patented method of use would change upon approval of the supplement, and FDA will continue to list this patent information for the product;

(B) If one or more existing patents for which information has already been submitted to FDA no longer claim the changed product, the applicant must submit a request under paragraph (f)(2)(iv) of this section to remove that patent information from the list at the time of approval of the supplement;

(C) If one or more existing drug substance (active ingredient), drug product (formulation and composition), or method-of-use patents claim the changed product for which approval is sought in the supplement and such patent information has not been submitted to FDA, the applicant must submit the patent information required under paragraph (c) of this section.

~~(iii) If the applicant submits a supplement for one of the changes listed under paragraph (d)(2)(i) of this section and no patents, including previously submitted patents, claim the changed product, it shall so certify.~~

~~(iv) The applicant shall comply with the requirements for amendment of formulation or composition and method of use patent information under paragraphs (c)(2)(ii) and (d)(3) of this section.~~

(3) ~~*Patent information deadline*~~*Newly issued patents*. If a patent is issued for a drug substance, drug product, or method of use after an ~~application~~ NDA is approved, the applicant ~~shall~~ must submit to ~~FDA~~FDA, as described in paragraph (d)(4) of this section, the required patent information within 30 days of the date of issuance of the patent. If the required patent information is no submitted within 30 days of the issuance of the patent, FDA will list the patent, but patent certifications or statements will be governed by the provisions regarding untimely filed patent information at §§ 314.50(i)(4) and (6) and 314.94(a)(12)(vi) and (viii).

(4) ~~*Copies*~~*Submission of Forms FDA 3542a and 3542* – (i) *Patent information submitted with the filling of an NDA, amendment or supplement.*~~.~~ The applicant ~~shall~~ must submit ~~two copies of each submission of patent information, an archival copy and a copy for the chemistry, manufacturing, and controls section of the review copy,~~patent information required by paragraphs (c)(1) and (c)(2)(i) of this section and § 314.50(h) or § 314.70(f) on Form FDA3542a ~~to~~ to the Central Document Room, Center for Drug Evaluation and Research, Food and Drug Administration, 5901-B Ammendale Rd., Beltsville, MD 20705-1266 or to FDA in an electronic format submission that complies with § 314.50(l)(5). ~~The applicant shall submit the patent information by letter separate from, but at the same time as, submission of the supplement.~~Form FDA3542a should not be submitted to the Orange Book Staff in the Office of Generic Drugs.

(ii) *Patent information submitted upon and after approval of an NDA supplement.* The applicant must submit patent information required by paragraphs (c)(1) and (c)(2)(ii) of this section on Form FDA 3542 to the Central Document Room, Center for Drug Evaluation and Research, Food and Drug Administration, 5901-B Ammendale Rd., Beltsville, MD 20705-1266, or to FDA in an electronic format submission that complies with § 314.50(l)(5). Form FDA 3542 should not be submitted to the Orange Book Staff in the Office of Generic Drugs.

(5) *Submission date.* Patent information ~~shall~~ will be considered to be submitted to ~~FDA~~FDA for purposes of paragraph (d)(3) of this section as of the earlier of the date the information submitted on Form FDA 3542 is date-stamped by ~~as of the date the information is received by~~ the Central Document Room, or officially received by FDA in an electronic format submission that complies with § 314.50(l)(5).

(6) *Identification.* Each submission of patent information, except information submitted with an original ~~application~~NDA, ~~and its mailing cover shall~~must bear prominent identification as to its contents, *i.e.*, "Patent Information," or, if submitted after approval of an ~~application~~NDA, "Time Sensitive Patent Information."

(e) *Public disclosure of patent information.* FDA will publish in the list the patent number and expiration date of each patent that is required to be, and is, submitted to FDA by an applicant, and for each method of use patent, the ~~approved indications or other conditions of use covered by a patent~~description of the method of use claimed by the patent as required by § 314.53(c)(2)(ii)(P)(3). FDA will publish such patent information upon approval of the ~~application~~NDA, or, if the patent information is submitted by the applicant after approval of an ~~application~~ NDA as provided under paragraph (d)(2) of this section, as soon as possible after the submission to the A~~a~~gency of the patent information. ~~Patent information submitted by the last working day of a month will be published in that month's supplement to the list. Patent information received by the Agency between monthly publication of supplements to the list will be placed on public display in FDA's Division of Freedom of Information.~~ A request for copies of the ~~file shall~~submitted patent information must be sent in writing to the Freedom of Information Staff at the address listed on the Agency's Web site at *http://www.fda.gov*. The submitted patent information, and requests to remove a patent or patent information from the list, may be subject to public disclosure.

(f) *Correction of patent information errors.* – (1) *Requests by persons other than the NDA holder.* If any person disputes the accuracy or relevance of patent information submitted to the A~~a~~gency under this section and published by FDA in the list, or believes that an ~~applicant~~ NDA holder has failed to submit required patent information, that person must first notify the A~~a~~gency in ~~writing stating the grounds for disagreement~~a written or electronic communication titled "314.53(f) Patent Listing Dispute." The patent listing dispute communication must include a statement of dispute that describes the specific grounds for disagreement regarding the accuracy or relevance of patent information for FDA to send to the applicable NDA holder. For a dispute regarding the accuracy or relevance of patent information regarding an approved method of using the drug product, this statement of dispute must be only a narrative description (no more than 250 words) of the person's interpretation of the scope of the patent. This statement of dispute must only

contain information for which the person consents to disclosure because FDA will send the text of the statement to the applicable NDA holder without review or redaction. The patent listing dispute communication should be directed to the Office 239 of Generic Drugs, OGD Document Room, Attention: Orange Book Staff, 7620 Standish Pl., Rockville, MD 20855, or to the Orange Book Staff at the email address listed on the Agency's Web site at http://www.fda.gov. ~~Such notification should be directed to the Office of Generic Drugs, OGD Document Room, Attention: Orange Book Staff, 7500 Standish Pl., Rockville, MD 20855. The agency will then request of the applicable new drug application holder that the correctness of the patent information or omission of patent information be confirmed. Unless the application holder withdraws or amends its patent information in response to FDA's request, the agency will not change the patent information in the list. If the new drug application holder does not change the patent information submitted to FDA, a 505(b)(2) application or an abbreviated new drug application under section 505(j) of the act submitted for a drug that is claimed by a patent for which information has been submitted must, despite any disagreement as to the correctness of the patent information, contain an appropriate certification for each listed patent.~~

(i) *Communication with the NDA holder--(A) Drug substance or drug product claim.* For requests submitted under this paragraph (f)(1) that are directed to the accuracy or relevance of submitted patent information regarding a drug substance or drug product claim, the Agency will send the statement of dispute to the applicable NDA holder. The NDA holder must confirm the correctness of the patent information and include the signed verification required by paragraph (c)(2)(ii)(R) of this section or withdraw or amend the patent information in accordance with paragraph (f)(2) of this section within 30 days of the date on which the Agency sends the statement of dispute. Unless the NDA holder withdraws or amends its patent information in response to the patent listing dispute, the Agency will not change the patent information in the Orange Book.

(B) *Method-of-use claim.* For requests submitted under this paragraph (f)(1) that are directed to the accuracy or relevance of submitted patent information regarding an approved method of using the drug product, FDA will send the statement of dispute to the NDA holder. The NDA holder must confirm the correctness of its description of the approved method of use claimed by the patent that has been included as the "Use Code" in the Orange Book, or withdraw or amend the patent information in accordance with paragraph (f)(2) of this section, provide a narrative description (no more than 250 words) of the NDA holder's interpretation of the scope of the patent that explains why the existing or amended "Use Code" describes only the specific approved method of use claimed by the patent for which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product, and include the signed verification

required by paragraph (c)(2)(ii)(R) of this section within 30 days of the date on which the Agency sends the statement of dispute. The narrative description must only contain information for which the NDA holder consents to disclosure because FDA will send the text of the statement to the person who submitted the patent listing dispute without review or redaction.

(*1*) If the NDA holder confirms the correctness of the patent information, provides the narrative description required by paragraph (f)(1)(i)(B) of this section, and includes the signed verification required by paragraph (c)(2)(ii)(R) of this section within 30 days of the date on which the Agency sends the statement of dispute, the Agency will not change the patent information in the Orange Book.

(*2*) If the NDA holder responds to the patent listing dispute with amended patent information in accordance with paragraph (f)(2) of this section, provides the narrative description required by paragraph (f)(1)(i)(B) of this section, and includes the signed verification required by paragraph (c)(2)(ii)(R) of this section within 30 days of the date on which the Agency sends the statement of dispute, FDA will update the Orange Book to reflect the amended patent information.

(ii) *Patent certification or statement during and after patent listing dispute.* A 505(b)(2) application or ANDA must contain an appropriate certification or statement for each listed patent, including the disputed patent, during and after the patent listing dispute.

(iii) *Information on patent listing disputes.* FDA will promptly post information on its Web site regarding whether a patent listing dispute has been submitted for a published description of a patented method of use for a drug product and whether the NDA holder has timely responded to the patent listing dispute.

(2) *Requests by the NDA holder--(i) Patents or patent claims that no longer meet the statutory requirements for listing.* If the NDA holder determines that a patent or patent claim no longer meets the requirements for listing in section 505(b)(1) or (c)(2) of the Federal Food, Drug, and Cosmetic Act (including if there has been a judicial finding of invalidity for a listed patent, from which no appeal has been or can be taken), the NDA holder is required to promptly notify FDA to amend the patent information or withdraw the patent or patent information and request that the patent or patent information be removed from the list. If the NDA holder is required by court order to amend patent information or withdraw a patent from the list, it must submit an amendment to its NDA that includes a copy of the order, within 14 days of the date the order was entered, to the Central Document Room, Center for Drug Evaluation and Research, Food and Drug Administration, 5901-B Ammendale Rd., Beltsville, MD 20705-1266. The amendment to the NDA must bear the identification described in paragraph (d)(6) of this section. FDA will remove a patent or patent information from

the list if there is no first applicant eligible for 180- day exclusivity based on a paragraph IV certification to that patent or after the 180-day exclusivity period of a first applicant based on that patent has expired or has been extinguished.

(ii) *Patent term restoration.* If the term of a listed patent is extended pursuant to 35 U.S.C. 156(e), the NDA holder must submit on Form FDA 3542 a correction to the expiration date of the patent. This correction must be submitted within 30 days of receipt of a certificate of extension as described in 35 U.S.C. 156(e)(1) or documentation of an extension of the term of the patent as described in 35 U.S.C. 156(e)(2).

(iii) *Submission of corrections or changes to patent information.* Corrections or changes to previously submitted patent information, other than withdrawal of a patent and requests to remove a patent from the list, must be submitted on Form FDA 3542 or 3542a, as appropriate, in an amendment or supplement to the NDA. The amendment or supplement to the NDA must bear the identification described in paragraph (d)(6) of this section. We will not accept the corrections or changes unless they are submitted on the appropriate forms.

(iv) *Submission of patent withdrawals and requests to remove a patent from the list.* Withdrawal of a patent and requests to remove a patent from the list must be submitted to the same addresses described in paragraph (d)(4)(ii) of this section, except that the withdrawal or request to remove a patent from the list is not required to be submitted on Form FDA 3542 and may be submitted by letter. Withdrawal of a patent and a request to remove a patent from the list must contain the following information:

(A) The NDA number to which the request applies;

(B) Each product(s) approved in the NDA to which the request applies; and

(C) The patent number.

21 C.F.R. § 314.54 – PROCEDURE FOR SUBMISSION OF A 505(B)(2) APPLICATION REQUIRING INVESTIGATIONS FOR APPROVAL OF A NEW INDICATION FOR, OR OTHER CHANGE FROM, A LISTED DRUG.

(a) The ~~act~~ Federal Food, Drug, and Cosmetic Act does not permit approval of an ~~abbreviated new drug application~~ANDA for a new indication, nor does it permit approval of other changes in a listed drug if investigations, other than bioavailability or bioequivalence studies, are essential to the approval of the change. Any person seeking approval of a drug product that represents a modification of a listed drug (e.g., a new

indication or new dosage form) and for which investigations, other than bioavailability or bioequivalence studies, are essential to the approval of the changes may, except as provided in paragraph (b) of this section, submit a 505(b)(2) application. This 505(b)(2) application need contain only that information needed to support the modification(s) of the listed drug.

(1) The applicant shall submit a complete archival copy of the application that contains the following:

(i) The information required under § 314.50(a), (b), (c), (d)(1), (d)(3), (e), and (g), except that § 314.50(d)(1)(ii)(*c*) shall contain the proposed or actual master production record, including a description of the equipment, to be used for the manufacture of a commercial lot of the drug product.

(ii) The information required under § 314.50 (d)(2), (d)(4) (if an anti-infective drug), (d)(5), (d)(6), and (f) as needed to support the safety and effectiveness of the drug product.

(iii) Identification of ~~the~~ each listed drug for which FDA has made a finding of safety and effectiveness and on which finding the applicant relies in seeking approval of its proposed drug product by established name, if any, proprietary name, dosage form, strength, route of administration, name of listed drug's application holder, and listed drug's approved ~~application~~ NDA number. The listed drug(s) identified as relied upon must include a drug product approved in an NDA that:

(A) Is pharmaceutically equivalent to the drug product for which the original 505(b)(2) application is submitted; and

(B) Was approved before the original 505(b)(2) application was submitted.

(iv) If the applicant is seeking approval only for a new indication and not for the indications approved for the listed drug on which the applicant relies, a certification so stating.

(v) Any patent information required under section 505(b)(1) of the ~~act~~ Federal Food, Drug, and Cosmetic Act with respect to any patent which claims the drug for which approval is sought or a method of using such drug and to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.

(vi) Any patent certification or statement required under section 505(b)(2) of the ~~act~~Federal Food, Drug, Cosmetic Act ~~-~~ with respect to any relevant patents that claim the listed drug(s) ~~or that claim any other drugs~~ on which investigations relied on by the applicant for approval of the application were conducted, or that claim a use for the listed or other drug(s). A 505(b)(2) applicant seeking approval of a drug that is pharmaceutically equivalent to a listed drug approved in an NDA implicitly relies upon

one such pharmaceutically equivalent listed drug.

(vii) If the applicant believes the change for which it is seeking approval is entitled to a period of exclusivity, the information required under § 314.50(j).

(2) The applicant ~~shall~~ must submit a review copy that contains the technical sections described in § 314.50(d)(1), except that section described in § 314.50(d)(1)(ii)(*c*) ~~shall~~ must contain the proposed or actual master production record, including a description of the equipment, to be used for the manufacture of a commercial lot of the drug product, and ~~paragraph~~ § 314.50(d)(3), and the technical sections described in ~~paragraphs~~ § 314.50(d)(2), (d)(4) ~~, (d)(5),~~through (d)(6), and (f) when needed to support the modification. Each of the technical sections in the review copy is required to be separately bound with a copy of the information required under § 314.50 (a), (b), and (c) and a copy of the proposed labeling.

(3) The information required by § 314.50 (d)(2), (d)(4) (if an anti-infective drug), (d)(5), (d)(6), and (f) for the listed drug on which the applicant relies shall be satisfied by reference to the listed drug under paragraph (a)(1)(iii) of this section.

(4) The applicant ~~shall~~ must submit a field copy of the 505(b)(2) application that contains the technical section described in § 314.50(d)(1), a copy of the information required under § 314.50(a) and (c), and certification that the field copy is a true copy of the technical section described in § 314.50(d)(1) contained in the archival and review copies of the 505(b)(2) application.

(b) A 505(b)(2)~~n~~ application may not be submitted under this section for a drug product whose only difference from ~~the reference~~a listed drug is that:

(1) The extent to which its active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the ~~reference~~ listed drug; or

(2) 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 reference listed drug.

21 C.F.R. § 314.60 – AMENDMENTS TO AN UNAPPROVED APPLICATION, SUPPLEMENT, OR RESUBMISSION

(a) *Submission of NDA.* FDA generally assumes that when an original ~~application~~NDA, supplement to an approved ~~application~~NDA, or resubmission of an ~~application~~ NDA or supplement is submitted to the ~~a~~Agency for review, the applicant believes that the ~~a~~Agency can approve the ~~application~~NDA, supplement, or

resubmission as submitted. However, the applicant may submit an amendment to an ~~application~~ NDA, supplement, or resubmission that has been filed under § 314.101 but is not yet approved.

(b)(1) *Submission of a major amendment.* Submission of a major amendment to an original application, efficacy supplement, or resubmission of an application or efficacy supplement within 3 months of the end of the initial review cycle constitutes an agreement by the applicant under section 505(c) of the act to extend the initial review cycle by 3 months. (For references to a resubmission of an application or efficacy supplement in paragraph (b) of this section, the timeframe for reviewing the resubmission is the "review cycle" rather than the "initial review cycle.") FDA may instead defer review of the amendment until the subsequent review cycle. If the agency extends the initial review cycle for an original application, efficacy supplement, or resubmission under this paragraph, the division responsible for reviewing the application, supplement, or resubmission will notify the applicant of the extension. The initial review cycle for an original application, efficacy supplement, or resubmission of an application or efficacy supplement may be extended only once due to submission of a major amendment. FDA may, at its discretion, review any subsequent major amendment during the initial review cycle (as extended) or defer review until the subsequent review cycle.

(2) Submission of a major amendment to an original application, efficacy supplement, or resubmission of an application or efficacy supplement more than 3 months before the end of the initial review cycle will not extend the cycle. FDA may, at its discretion, review such an amendment during the initial review cycle or defer review until the subsequent review cycle.

(3) Submission of an amendment to an original application, efficacy supplement, or resubmission of an application or efficacy supplement that is not a major amendment will not extend the initial review cycle. FDA may, at its discretion, review such an amendment during the initial review cycle or defer review until the subsequent review cycle.

(4) Submission of a major amendment to a manufacturing supplement within 2 months of the end of the initial review cycle constitutes an agreement by the applicant under section 505(c) of the act to extend the initial review cycle by 2 months. FDA may instead defer review of the amendment until the subsequent review cycle. If the agency extends the initial review cycle for a manufacturing supplement under this paragraph, the division responsible for reviewing the supplement will notify the applicant of the extension. The initial review cycle for a manufacturing supplement may be extended only once due to submission of a major amendment. FDA may, at its discretion, review any subsequent major amendment during the initial review cycle (as extended) or defer review until the subsequent review cycle.

(5) Submission of an amendment to a supplement other than an efficacy or manufacturing supplement will not extend the initial review cycle. FDA may, at its discretion, review such an amendment during the initial review cycle or defer review until the subsequent review cycle.

(6) A major amendment may not include data to support an indication or claim that was not included in the original application, supplement, or resubmission, but it may include data to support a minor modification of an indication or claim that was included in the original application, supplement, or resubmission.

(7) When FDA defers review of an amendment until the subsequent review cycle, the agency will notify the applicant of the deferral in the complete response letter sent to the applicant under § 314.110 of this part.~~(c)(1) An unapproved application may not be amended if all of the following conditions apply:~~

(c)(1) *Limitation on certain amendments.* An unapproved application may not be amended if all of the following conditions apply:

(i) The unapproved application is for a drug for which a previous application has been approved and granted a period of exclusivity in accordance with section 505(c)(3)(D)(ii) of the act that has not expired;

(ii) The applicant seeks to amend the unapproved application to include a published report of an investigation that was conducted or sponsored by the applicant entitled to exclusivity for the drug;

(iii) The applicant has not obtained a right of reference or use to the investigation described in paragraph (c)(1)(ii) of this section; and

(iv) The report of the investigation described in paragraph (c)(1)(ii) of this section would be essential to the approval of the unapproved application.

(2) The submission of an amendment described in paragraph (c)(1) of this section will cause the unapproved application to be deemed to be withdrawn by the applicant under § 314.65 on the date of receipt by FDA of the amendment. The amendment will be considered a resubmission of the application, which may not be accepted except as provided in accordance with section 505(c)(3)(D)(ii) of the act.

(d) *Field Copy.* The applicant ~~shall~~ must submit a field copy of each amendment to a section of the NDA described in § 314.50(d)(1). The applicant ~~shall~~ must include in its submission of each such amendment to FDA a statement certifying that a field copy of the amendment has been sent to the applicant's home FDA district office.

(e) *Different drug.* An applicant may not amend a 505(b)(2) application to seek approval of a drug that is a different drug from the drug in the original submission of the 505(b)(2) application. For purposes of

this paragraph (e), a drug is a different drug if it has been modified to have a different active ingredient, different route of administration, different dosage form, or difference in excipients that requires either a separate clinical study to establish safety or effectiveness or, for topical products, that requires a separate in vivo demonstration of bioequivalence. However, notwithstanding the limitation described in this paragraph (e), an applicant may amend the 505(b)(2) application to seek approval of a different strength.

(f) *Patent certification requirements.* (1) An amendment to a 505(b)(2) application is required to contain an appropriate patent certification or statement described in § 314.50(i) or a recertification for a previously submitted paragraph IV certification if approval is sought for any of the following types of amendments:

(i) To add a new indication or other condition of use;

(ii) To add a new strength;

(iii) To make other than minor changes in product formulation; or

(iv) To change the physical form or crystalline structure of the active ingredient.

(2) If the amendment to the 505(b)(2) application does not contain a patent certification or statement, the applicant must verify that the proposed change described in the amendment is not one of the types of amendments described in paragraph (f)(1) of this section.

21 C.F.R. § 314.70 – SUPPLEMENTS AND OTHER CHANGES TO AN APPROVED APPLICATION

(a) *Changes to an approved application.* (1)(i) Except as provided in paragraph (a)(1)(ii) of this section, the applicant must notify FDA about each change in each condition established in an approved application beyond the variations already provided for in the application. The notice is required to describe the change fully. Depending on the type of change, the applicant must notify FDA about the change in a supplement under paragraph (b) or (c) of this section or by inclusion of the information in the annual report to the application under paragraph (d) of this section.

(ii) The submission and grant of a written request for an exception or alternative under § 201.26 of this chapter satisfies the applicable requirements in paragraphs (a) through (c) of this section. However, any grant of a request for an exception or alternative under § 201.26 of this chapter must be reported as part of the annual report to the application under paragraph (d) of this section.

(2) The NDA holder ~~of an approved application under section 505 of the act~~ must assess the effects of the change before distributing a drug product made with a manufacturing change.

(3) Notwithstanding the requirements of paragraphs (b) and (c) of this section, an applicant must make a change provided for in those paragraphs in accordance with a regulation or guidance that provides for a less burdensome notification of the change (for example, by submission of a supplement that does not require approval prior to distribution of the product or in an annual report).

(4) The applicant must promptly revise all promotional labeling and advertising to make it consistent with any labeling change implemented in accordance with paragraphs (b) and (c) of this section.

(5) Except for a supplement providing for a change in the labeling, the applicant must include in each supplement and amendment to a supplement providing for a change under paragraph (b) or (c) of this section a statement certifying that a field copy has been provided in accordance with § 314.440(a)(4).

(6) A supplement or annual report must include a list of all changes contained in the supplement or annual report. For supplements, this list must be provided in the cover letter.

(b) *Changes requiring supplement submission and approval prior to distribution of the product made using the change (major changes).* (1) A supplement must be submitted for any change in the drug substance, drug product, production process, quality controls, equipment, or facilities that has a substantial potential to have an adverse effect on the identity, strength, quality, purity, or potency of the drug product as these factors may relate to the safety or effectiveness of the drug product.

(2) These changes include, but are not limited to:

(i) Except those described in paragraphs (c) and (d) of this section, changes in the qualitative or quantitative formulation of the drug product, including inactive ingredients, or in the specifications provided in the approved application;

(ii) Changes requiring completion of studies in accordance with part 320 of this chapter to demonstrate the equivalence of the drug product to the drug product as manufactured without the change or to the reference listed drug;

(iii) Changes that may affect drug substance or drug product sterility assurance, such as changes in drug substance, drug product, or component sterilization method(s) or an addition, deletion, or substitution of steps in an aseptic processing operation;

(iv) Changes in the synthesis or manufacture of the drug substance that may affect the impurity profile and/or the physical, chemical, or biological properties of the drug substance;

(v) The following labeling changes:

(A) Changes in labeling, except those described in paragraphs (c)(6)(iii), (d)(2)(ix), or (d)(2)(x) of this section;

(B) If applicable, any change to a Medication Guide required under part 208 of this chapter, except for changes in the information specified in § 208.20(b)(8)(iii) and (b)(8)(iv) of this chapter; and

(C) Any change to the information required by § 201.57(a) of this chapter, with the following exceptions that may be reported in an annual report under paragraph (d)(2)(x) of this section:

(*1*) Removal of a listed section(s) specified in § 201.57(a)(5) of this chapter; and

(*2*) Changes to the most recent revision date of the labeling as specified in § 201.57(a)(15) of this chapter.

(vi) Changes in a drug product container closure system that controls the drug product delivered to a patient or changes in the type (e.g., glass to high density polyethylene (HDPE), HDPE to polyvinyl chloride, vial to syringe) or composition (e.g., one HDPE resin to another HDPE resin) of a packaging component that may affect the impurity profile of the drug product.

(vii) Changes solely affecting a natural product, a recombinant DNA-derived protein/polypeptide, or a complex or conjugate of a drug substance with a monoclonal antibody for the following:

(A) Changes in the virus or adventitious agent removal or inactivation method(s);

(B) Changes in the source material or cell line; and

(C) Establishment of a new master cell bank or seed.

(viii) Changes to a drug product under an application that is subject to a validity assessment because of significant questions regarding the integrity of the data supporting that application.

(3) The applicant must obtain approval of a supplement from FDA prior to distribution of a drug product made using a change under paragraph (b) of this section. Except for submissions under paragraph (e) of this section, the following information must be contained in the supplement:

(i) A detailed description of the proposed change;

(ii) The drug product(s) involved;

(iii) The manufacturing site(s) or area(s) affected;

(iv) A description of the methods used and studies performed to assess the effects of the change;

(v) The data derived from such studies;

(vi) For a natural product, a recombinant DNA-derived protein/polypeptide, or a complex or conjugate of a drug substance with a monoclonal antibody, relevant validation protocols and a list of relevant standard operating procedures must be provided in addition to the requirements in paragraphs (b)(3)(iv) and (b)(3)(v) of this section; and

(vii) For sterilization process and test methodologies related to sterilization process validation, relevant validation protocols and a list of relevant standard operating procedures must be provided in addition to the requirements in paragraphs (b)(3)(iv) and (b)(3)(v) of this section.

(4) An applicant may ask FDA to expedite its review of a supplement for public health reasons or if a delay in making the change described in it would impose an extraordinary hardship on the applicant. Such a supplement and its mailing cover should be plainly marked: "Prior Approval Supplement-Expedited Review Requested."

(c) *Changes requiring supplement submission at least 30 days prior to distribution of the drug product made using the change (moderate changes).* (1) A supplement must be submitted for any change in the drug substance, drug product, production process, quality controls, equipment, or facilities that has a moderate potential to have an adverse effect on the identity, strength, quality, purity, or potency of the drug product as these factors may relate to the safety or effectiveness of the drug product. If the supplement provides for a labeling change under paragraph (c)(6)(iii) of this section, 12 copies of the final printed labeling must be included.

(2) These changes include, but are not limited to:

(i) A change in the container closure system that does not affect the quality of the drug product, except those described in paragraphs (b) and (d) of this section; and

(ii) Changes solely affecting a natural protein, a recombinant DNA-derived protein/polypeptide or a complex or conjugate of a drug substance with a monoclonal antibody, including:

(A) An increase or decrease in production scale during finishing steps that involves different equipment; and

(B) Replacement of equipment with that of a different design that does not affect the process methodology or process operating parameters.

(iii) Relaxation of an acceptance criterion or deletion of a test to comply with an official compendium that is consistent with FDA statutory and regulatory requirements.

(3) A supplement submitted under paragraph (c)(1) of this section is required to give a full explanation of the basis for the change and identify the date on which the change is to be made. The supplement must be labeled "Supplement—Changes Being Effected in 30 Days" or, if applicable under paragraph (c)(6) of this section, "Supplement—Changes Being Effected."

(4) Pending approval of the supplement by FDA, except as provided in paragraph (c)(6) of this section, distribution of the drug product made using the change may begin not less than 30 days after receipt of the supplement by FDA. The information listed in paragraphs (b)(3)(i) through (b)(3)(vii) of this section must be contained in the supplement.

(5) The applicant must not distribute the drug product made using the change if within 30 days following FDA's receipt of the supplement, FDA informs the applicant that either:

(i) The change requires approval prior to distribution of the drug product in accordance with paragraph (b) of this section; or

(ii) Any of the information required under paragraph (c)(4) of this section is missing; the applicant must not distribute the drug product made using the change until the supplement has been amended to provide the missing information.

(6) The agency may designate a category of changes for the purpose of providing that, in the case of a change in such category, the holder of an approved application may commence distribution of the drug product involved upon receipt by the agency of a supplement for the change. These changes include, but are not limited to:

(i) Addition to a specification or changes in the methods or controls to provide increased assurance that the drug substance or drug product will have the characteristics of identity, strength, quality, purity, or potency that it purports or is represented to possess;

(ii) A change in the size and/or shape of a container for a nonsterile drug product, except for solid dosage forms, without a change in the labeled amount of drug product or from one container closure system to another;

(iii) Changes in the labeling to reflect newly acquired information, except for changes to the information required in § 201.57(a) of this chapter (which must be made under paragraph (b)(2)(v)(C) of this section), to accomplish any of the following:

(A) To add or strengthen a contraindication, warning, precaution, or adverse reaction for which the evidence of a causal association satisfies the standard for inclusion in the labeling under § 201.57(c) of this chapter;

(B) To add or strengthen a statement about drug abuse, dependence, psychological effect, or overdosage;

(C) To add or strengthen an instruction about dosage and administration that is intended to increase the safe use of the drug product;

(D) To delete false, misleading, or unsupported indications for use or claims for effectiveness; or

(E) Any labeling change normally requiring a supplement submission and approval prior to distribution of the drug product that FDA specifically requests be submitted under this provision.

(7) If the agency disapproves the supplemental application, it may order the manufacturer to cease distribution of the drug product(s) made with the manufacturing change.

(d) *Changes to be described in an annual report (minor changes).* (1) Changes in the drug substance, drug product, production process, quality controls, equipment, or facilities that have a minimal potential to have an adverse effect on the identity, strength, quality, purity, or potency of the drug product as these factors may relate to the safety or effectiveness of the drug product must be documented by the applicant in the next annual report in accordance with § 314.81(b)(2).

(2) These changes include, but are not limited to:

(i) Any change made to comply with a change to an official compendium, except a change described in paragraph (c)(2)(iii) of this section, that is consistent with FDA statutory and regulatory requirements.

(ii) The deletion or reduction of an ingredient intended to affect only the color of the drug product;

(iii) Replacement of equipment with that of the same design and operating principles except those equipment changes described in paragraph (c) of this section;

(iv) A change in the size and/or shape of a container containing the same number of dosage units for a nonsterile solid dosage form drug product, without a change from one container closure system to another;

(v) A change within the container closure system for a nonsterile drug product, based upon a showing of equivalency to the approved system under a protocol approved in the application or published in an official compendium;

(vi) An extension of an expiration dating period based upon full shelf life data on production batches obtained from a protocol approved in the application;

(vii) The addition or revision of an alternative analytical procedure that provides the same or increased assurance of the identity, strength, quality, purity, or potency of the material being tested as the analytical procedure described in the approved application, or deletion of an alternative analytical procedure;

(viii) The addition by embossing, debossing, or engraving of a code imprint to a solid oral dosage form drug product other than a modified release dosage form, or a minor change in an existing code imprint;

(ix) A change in the labeling concerning the description of the drug product or in the information about how the drug product is supplied, that does not involve a change in the dosage strength or dosage form; and

(x) An editorial or similar minor change in labeling, including a change to the information allowed by paragraphs (b)(2)(v)(C)(*1*) and (*2*) of this section.

(3) For changes under this category, the applicant is required to submit in the annual report:

(i) A statement by the holder of the approved application that the effects of the change have been assessed;

(ii) A full description of the manufacturing and controls changes, including the manufacturing site(s) or area(s) involved;

(iii) The date each change was implemented;

(iv) Data from studies and tests performed to assess the effects of the change; and,

(v) For a natural product, recombinant DNA-derived protein/polypeptide, complex or conjugate of a drug substance with a monoclonal antibody, sterilization process or test methodology related to sterilization process validation, a cross-reference to relevant validation protocols and/or standard operating procedures.

(e) *Protocols.* An applicant may submit one or more protocols describing the specific tests and studies and acceptance criteria to be achieved to demonstrate the lack of adverse effect for specified types of manufacturing changes on the identity, strength, quality, purity, and potency of the drug product as these factors may relate to the safety or effectiveness of the drug product. Any such protocols, if not included in the approved application, or changes to an approved protocol, must be submitted as a supplement requiring approval from FDA prior to distribution of a drug product produced with the manufacturing change. The supplement, if approved, may subsequently justify a reduced reporting category for the particular change because the use of the protocol for that type of change reduces the potential risk of an adverse effect.

(f) *Patent information.* The applicant must comply with the patent information requirements under section 505(c)(2) of the ~~act~~Federal Food, Drug, and Cosmetic Act and § 314.53.

(g) *Claimed exclusivity.* If an applicant claims exclusivity under § 314.108 upon approval of a supplement for change to its previously approved drug product, the applicant must include with its supplement the information required under § 314.50(j).

(h) *Different drug.* An applicant may not supplement a 505(b)(2) application to seek approval of a drug that is a different drug from the drug in the approved 505(b)(2) application. 248 For purposes of this paragraph (h), a drug is a different drug if it has been modified to have a different active ingredient, different route of administration, different dosage form, or difference in excipients that requires either a separate clinical study to establish safety or effectiveness or, for topical products, that requires a separate in vivo demonstration of bioequivalence. However, notwithstanding the limitation described in this paragraph (h), an applicant may supplement the 505(b)(2) application to seek approval of a different strength.

21 C.F.R. § 314.90 – WAIVERS

(a) An applicant may ask the Food and Drug Administration to waive under this section any requirement that applies to the applicant under §§ 314.50 through 314.81. An applicant may ask FDA to waive under § 314.126(c) any criteria of an adequate and well-controlled study described in § 314.126(b). A waiver request under this section is required to be submitted with supporting documentation in an application, or in an amendment or supplement to an application. The waiver request is required to contain one of the following:

(1) An explanation why the applicant's compliance with the requirement is unnecessary or cannot be achieved;

(2) A description of an alternative submission that satisfies the purpose of the requirement; or

(3) Other information justifying a waiver.

(b) FDA may grant a waiver if it finds one of the following:

(1) The applicant's compliance with the requirement is unnecessary for the agency to evaluate the application or compliance cannot be achieved;

(2) The applicant's alternative submission satisfies the requirement; or

(3) The applicant's submission otherwise justifies a waiver.

(c) If FDA grants the applicant’s waiver request with respect to a requirement under §§ 314.50 through 314.81, the waived requirement will not constitute a basis for refusal to approve an NDA under § 314.125.

21 C.F.R. § 314.93 – PETITION TO REQUEST A CHANGE FROM A LISTED DRUG

(a) The only changes from a listed drug for which the agency will accept a petition under this section are those changes described in paragraph (b) of this section. Petitions to submit abbreviated new drug applications for other changes from a listed drug will not be approved.

(b) A person who wants to submit an abbreviated new drug application for a drug product which is not identical to a listed drug in route of administration, dosage form, and strength, or in which one active ingredient is substituted for one of the active ingredients in a listed combination drug, must first obtain permission from FDA to submit such an abbreviated application.

(c) To obtain permission to submit an abbreviated new drug application for a change described in paragraph (b) of this section, a person must submit and obtain approval of a petition requesting the change. A person seeking permission to request such a change from a reference listed drug shall submit a petition in accordance with § 10.20 of this chapter and in the format specified in § 10.30 of this chapter. The petition shall contain the information specified in § 10.30 of this chapter and any additional information required by this section. If any provision of § 10.20 or § 10.30 of this chapter is inconsistent with any provision of this section, the provisions of this section apply.

(d) The petitioner shall identify a listed drug and include a copy of the proposed labeling for the drug product that is the subject of the petition and a copy of the approved labeling for the listed drug. The petitioner may, under limited circumstances, identify more than one listed drug, for example, when the proposed drug product is a combination product that differs from the combination reference listed drug with regard to an active ingredient, and the different active ingredient is an active ingredient of a listed drug. The petitioner shall also include information to show that:

(1) The active ingredients of the proposed drug product are of the same pharmacological or therapeutic class as those of the reference listed drug.

(2) The drug product can be expected to have the same therapeutic effect as the reference listed drug when administered to patients for each condition of use in the reference listed drug's labeling for which the applicant seeks approval.

(3) If the proposed drug product is a combination product with one different active ingredient, including a different ester or salt, from the reference listed drug, that the different active ingredient has previously been approved in a listed drug or is a drug that does not meet the definition of “new drug” in section 201(b) of the act.

(e) No later than 90 days after the date a petition that is permitted under paragraph (a) of this section is submitted, FDA will approve or disapprove the petition.

(1) FDA will approve a petition properly submitted under this section unless it finds that:

(i) Investigations must be conducted to show the safety and effectiveness of the drug product or of any of its active ingredients, its route of administration, dosage form, or strength which differs from the reference listed drug; or

(ii) For a petition that seeks to change an active ingredient, the drug product that is the subject of the petition is not a combination drug; or

(iii) For a combination drug product that is the subject of the petition and has an active ingredient different from the reference listed drug:

(A) The drug product may not be adequately evaluated for approval as safe and effective on the basis of the information required to be submitted under § 314.94; or

(B) The petition does not contain information to show that the different active ingredient of the drug product is of the same pharmacological or therapeutic class as the ingredient of the reference listed drug that is to be changed and that the drug product can be expected to have the same therapeutic effect as the reference listed drug when administered to patients for each condition of use in the listed drug's labeling for which the applicant seeks approval; or

(C) The different active ingredient is not an active ingredient in a listed drug or a drug that meets the requirements of section 201(p) of the act; or

(D) The remaining active ingredients are not identical to those of the listed combination drug; or

(iv) Any of the proposed changes from the listed drug would jeopardize the safe or effective use of the product so as to necessitate significant labeling changes to address the newly introduced safety or effectiveness problem; or

(v) FDA has determined that the reference listed drug has been withdrawn from sale for safety or effectiveness reasons under § 314.161, or the reference listed drug has been voluntarily withdrawn from sale and the agency has not determined whether the withdrawal is for safety or effectiveness reasons.

(2) For purposes of this paragraph, "investigations must be conducted" means that information derived from animal or clinical studies is necessary to show that the drug product is safe or effective. Such information may be contained in published or unpublished reports.

(3) If FDA approves a petition submitted under this section, the agency's response may describe what additional information, if any, will be required to support an abbreviated new drug application for the drug product. FDA may, at any time during the course of its review of an abbreviated new drug application, request additional

information required to evaluate the change approved under the petition.

(vi) A drug product is approved in an NDA for the change described in the petition.

(f) FDA may withdraw approval of a petition if the agency receives any information demonstrating that the petition no longer satisfies the conditions under paragraph (e) of this section.

(2) If, after approval of a petition and before approval of an ANDA submitted pursuant to the approved petition, a drug product is approved in an NDA for the change described in the petition, the petition and the listed drug identified in the petition can no longer be the basis for ANDA submission, irrespective of whether FDA has withdrawn approval of the petition. A person seeking approval for such drug product must submit a new ANDA that identifies the pharmaceutically equivalent reference listed drug as the basis for ANDA submission and comply with applicable regulatory requirements.

21 C.F.R. § 314.94 – CONTENT AND FORMAT OF AN ~~ABBREVIATED APPLICATION~~ANDA

~~Abbreviated applications~~ANDAs are required to be submitted in the form and contain the information required under this section. Three copies of the ~~application~~ ANDA are required, an archival copy, a review copy, and a field copy. FDA will maintain guidance documents on the format and content of ~~applications~~ ANDAs to assist applicants in their preparation.

(a) ~~*Abbreviated new drug applications*~~*ANDAs*. Except as provided in paragraph (b) of this section, the applicant shall submit a complete archival copy of the abbreviated new drug application that includes the following:

(1) *Application form.* The applicant shall submit a completed and signed application form that contains the information described under § 314.50(a)(1), (a)(3), (a)(4), and (a)(5). The applicant shall state whether the submission is an abbreviated application under this section or a supplement to an abbreviated application under § 314.97.

(2) *Table of contents.* The archival copy of the ~~abbreviated new drug application~~ANDA is required to contain a table of contents that shows the volume number and page number of the contents of the submission.

(3) *Basis for ANDA~~abbreviated new drug application~~ submission.* An ANDA~~abbreviated new drug application~~ must refer to a listed drug. Ordinarily, that listed drug will be the drug product selected

by the ~~a~~Agency as the reference standard for conducting bioequivalence testing. The ANDA~~application shall~~ must contain:

(i) The name of the reference listed drug, including its dosage form and strength. For an ANDA ~~abbreviated new drug application~~ based on an approve~~r~~d petition under § 10.30 of this chapter or § 314.93, the reference listed drug must be the same as the listed drug approved in the petition.

(ii) A statement as to whether, according to the information published in the list, the reference listed drug is entitled to a period of marketing exclusivity under section 505(j)(5~~4~~)(F~~D~~) of the Federal Food, Drug, and Cosmetic Act~~act~~.

(iii) For an ANDA~~abbreviated new drug application~~ based on an approved petition under § 10.30 of this chapter or § 314.93, a reference to the FDA-assigned docket number for the petition and a copy of FDA's correspondence approving the petition.

(4) *Conditions of use.* (i) A statement that the conditions of use prescribed, recommended, or suggested in the labeling proposed for the drug product have been previously approved for the reference listed drug.

(ii) A reference to the applicant's annotated proposed labeling and to the currently approved labeling for the reference listed drug provided under paragraph (a)(8) of this section.

(5) *Active ingredients.* (i) For a single-active-ingredient drug product, information to show that the active ingredient is the same as that of the reference single-active-ingredient listed drug, as follows:

(A) A statement that the active ingredient of the proposed drug product is the same as that of the reference listed drug.

(B) A reference to the applicant's annotated proposed labeling and to the currently approved labeling for the reference listed drug provided under paragraph (a)(8) of this section.

(ii) For a combination drug product, information to show that the active ingredients are the same as those of the reference listed drug except for any different active ingredient that has been the subject of an approved petition, as follows:

(A) A statement that the active ingredients of the proposed drug product are the same as those of the reference listed drug, or if one of the active ingredients differs from one of the active ingredients of the reference listed drug and the abbreviated application is submitted under the approval of a petition under § 314.93 to vary such active ingredient, information to show that the other active ingredients of the drug product are the same as the other active ingredients of the reference listed drug, information to show that the different active ingredient is an active ingredient of another listed drug or of a drug that does not meet the definition of “new drug” in section 201(p) of the act, and such other information

about the different active ingredient that FDA may require.

(B) A reference to the applicant's annotated proposed labeling and to the currently approved labeling for the reference listed drug provided under paragraph (a)(8) of this section.

(6) *Route of administration, dosage form, and strength.* (i) Information to show that the route of administration, dosage form, and strength of the drug product are the same as those of the reference listed drug except for any differences that have been the subject of an approved petition, as follows:

(A) A statement that the route of administration, dosage form, and strength of the proposed drug product are the same as those of the reference listed drug.

(B) A reference to the applicant's annotated proposed labeling and to the currently approved labeling for the reference listed drug provided under paragraph (a)(8) of this section.

(ii) If the route of administration, dosage form, or strength of the drug product differs from the reference listed drug and the abbreviated application is submitted under an approved petition under § 314.93, such information about the different route of administration, dosage form, or strength that FDA may require.

(7) *Bioequivalence.* (i) Information that shows that the drug product is bioequivalent to the reference listed drug upon which the applicant relies. A complete study report must be submitted for the bioequivalence study upon which the applicant relies for approval. For all other bioequivalence studies conducted on the same drug product formulation as defined in § 320.1(g) of this chapter, the applicant must submit either a complete or summary report. If a summary report of a bioequivalence study is submitted and FDA determines that there may be bioequivalence issues or concerns with the product, FDA may require that the applicant submit a complete report of the bioequivalence study to FDA; or

(ii) If the ANDA~~abbreviated new drug application~~ is submitted under a petition approved under § 314.93, the results of any bioavailability of bioequivalence testing required by the ~~a~~Agency, or any other information required by the ~~a~~Agency to show that the active ingredients of the proposed drug product are of the same pharmacological or therapeutic class as those in the reference listed drug and that the proposed drug product can be expected to have the same therapeutic effect as the reference listed drug. If the proposed drug product contains a different active ingredient than the reference listed drug, FDA will consider the proposed drug product to have the same therapeutic effect as the reference listed drug if the applicant provides information demonstrating that:

(A) There is an adequate scientific basis for determining that substitution of the specific proposed dose of the different active ingredient for the dose of the member of the same pharmacological or therapeutic class in

the reference listed drug will yield a resulting drug product whose safety and effectiveness have not been adversely affected.

(B) The unchanged active ingredients in the proposed drug product are bioequivalent to those in the reference listed drug.

(C) The different active ingredient in the proposed drug product is bioequivalent to an approved dosage form containing that ingredient and approved for the same indication as the proposed drug product or is bioequivalent to a drug product offered for that indication which does not meet the definition of "new drug" under section 201(p) of the act.

(iii) For each in vivo or in vitro bioequivalence study contained in the ANDA:~~abbreviated new drug application,~~

(A) ~~a~~ A description of the analytical and statistical methods used in each study; and

(B) ~~a statement w~~With respect to each study involving human subject, a statement that the study either was ~~that it either was~~ conducted in compliance with the institutional review board regulations in part 56 of this chapter, or was not subject to the regulations under § 56.104 or § 56.105 of this chapter, and that ~~each study~~it was conducted in compliance with the informed consent regulations in part 50 of this chapter.

(8) *Labeling*—(i) *Listed drug labeling.* A copy of the currently approved labeling (including, if applicable, any Medication Guide required under part 208 of this chapter) for the listed drug referred to in the abbreviated new drug application, if the abbreviated new drug application relies on a reference listed drug.

(ii) *Copies of proposed labeling.* Copies of the label and all labeling for the drug product including, if applicable, any Medication Guide required under part 208 of this chapter (4 copies of draft labeling or 12 copies of final printed labeling).

(iii) *Statement on proposed labeling.* A statement that the applicant's proposed labeling including, if applicable, any Medication Guide required under part 208 of this chapter is the same as the labeling of the reference listed drug except for differences annotated and explained under paragraph (a)(8)(iv) of this section.

(iv) *Comparison of approved and proposed labeling.* A side-by-side comparison of the applicant's proposed labeling including, if applicable, any Medication Guide required under part 208 of this chapter with the approved labeling for the reference listed drug with all differences annotated and explained. Labeling (including the container label, package insert, and, if applicable, Medication Guide) proposed for the drug product must be the same as the labeling approved for the reference listed drug, except for changes required because of differences approved under a petition filed under § 314.93 or because the drug product and the reference listed drug are produced or distributed by

different manufacturers. Such differences between the applicant's proposed labeling and labeling approved for the reference listed drug may include differences in expiration date, formulation, bioavailability, or pharmacokinetics, labeling revisions made to comply with current FDA labeling guidelines or other guidance, or omission of an indication or other aspect of labeling protected by patent or accorded exclusivity under section 505(j)(5)(F) of the act.

(9) *Chemistry, manufacturing, and controls.* (i) The information required under § 314.50(d)(1), except that the information required under § 314.50(d)(1)(ii)(*c*) ~~shall~~ must contain the proposed or actual master production record, including a description of the equipment, to be used for the manufacture of a commercial lot of the drug product.

(ii) *Inactive ingredients.* Unless otherwise stated in paragraphs (a)(9)(iii) through (a)(9)(v) of this section, an applicant shall identify and characterize the inactive ingredients in the proposed drug product and provide information demonstrating that such inactive ingredients do not affect the safety or efficacy of the proposed drug product.

(iii) *Inactive ingredient changes permitted in drug products intended for parenteral use.* Generally, a drug product intended for parenteral use shall contain the same inactive ingredients and in the same concentration as the reference listed drug identified by the applicant under paragraph (a)(3) of this section. However, an applicant may seek approval of a drug product that differs from the reference listed drug in preservative, buffer, or antioxidant provided that the applicant identifies and characterizes the differences and provides information demonstrating that the differences do not affect the safety or efficacy of the proposed drug product.

(iv) *Inactive ingredient changes permitted in drug products intended for ophthalmic or otic use.* Generally, a drug product intended for ophthalmic or otic use shall contain the same inactive ingredients and in the same concentration as the reference listed drug identified by the applicant under paragraph (a)(3) of this section. However, an applicant may seek approval of a drug product that differs from the reference listed drug in preservative, buffer, substance to adjust tonicity, or thickening agent provided that the applicant identifies and characterizes the differences and provides information demonstrating that the differences do not affect the safety or efficacy of the proposed drug product, except that, in a product intended for ophthalmic use, an applicant may not change a buffer or substance to adjust tonicity for the purpose of claiming a therapeutic advantage over or difference from the listed drug, e.g., by using a balanced salt solution as a diluent as opposed to an isotonic saline solution, or by making a significant change in the pH or other change that may raise questions of irritability.

(v) *Inactive ingredient changes permitted in drug products intended for*

topical use. Generally, a drug product intended for topical use, solutions for aerosolization or nebulization, and nasal solutions shall contain the same inactive ingredients as the reference listed drug identified by the applicant under paragraph (a)(3) of this section. However, an abbreviated application may include different inactive ingredients provided that the applicant identifies and characterizes the differences and provides information demonstrating that the differences do not affect the safety or efficacy of the proposed drug product.

(10) *Samples.* The information required under § 314.50(e)(1) and (e)(2)(i). Samples need not be submitted until requested by FDA.

(11) *Other.* The information required under § 314.50(g).

(12) *Patent certification*—(i) *Patents claiming drug substance, drug product, or method of use.* (A) An appropriate patent certification or statement ~~Except as provided in paragraph (a)(12)(iv) of this section, a certification~~ with respect to each patent issued by the United States Patent and Trademark Office that, in the opinion of the applicant and to the best of its knowledge, claims the reference listed drug or that claims a use of such listed drug for which the applicant is seeking approval under section 505(j) of the ~~act~~ Federal Food, Drug, and Cosmetic Act and for which information is required to be filed under section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act ~~act~~ and § 314.53. For each such patent, the applicant ~~shall~~ must provide the patent number and certify, in its opinion and to the best of its knowledge, one of the following circumstances:

(*1*) That the patent information has not been submitted to FDA. The applicant shall entitle such a certification "Paragraph I Certification";

(*2*) That the patent has expired. The applicant shall entitle such a certification "Paragraph II Certification";

(*3*) The date on which the patent will expire. The applicant shall entitle such a certification "Paragraph III Certification"; or

(*4*)(*i*) That the patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the ~~abbreviated application~~ANDA is submitted. The applicant ~~shall~~ must entitle such a certification "Paragraph IV Certification". This certification ~~shall~~ must be submitted in the following form:

I, (*NAME OF APPLICANT*), CERTIFY THAT PATENT NO. _____ (*IS INVALID, UNENFORCEABLE, OR WILL NOT BE INFRINGED BY THE MANUFACTURE, USE, OR SALE OF*) (*NAME OF PROPOSED DRUG PRODUCT*) FOR WHICH THIS ANDA~~APPLICATION~~ IS SUBMITTED.

(*ii*)The certification ~~shall~~ must be accompanied by a statement that the applicant will comply with the requirements

under § 314.95(a) with respect to providing a notice to each owner of the patent or ~~their~~ its representatives and to the NDA holder (or, if the NDA holder does not reside or maintain a place of business within the United States, its attorney, agent, or other authorized official) ~~of the approved application~~ for the listed drug, with the requirements under § 314.95(b) with respect to sending the notice, and with the requirements under § 314.95(c) with respect to the content of the notice.

(B) If the ANDA~~abbreviated new drug application~~ refers to a listed drug that is itself a licensed generic product of a patented drug first approved under section 505(b) of the ~~act~~Federal Food, Drug, and Cosmetic Act, ~~the~~ an appropriate patent certification or statement under paragraph (a)(12)(i) and/or (iii) of this section with respect to each patent that claims the first-approved patented drug or that claims a use for such drug.

(ii) *No relevant patents.* If, in the opinion of the applicant and to the best of its knowledge, there are no patents described in paragraph (a)(12)(i) of this section, a certification in the following form:

IN THE OPINION AND TO THE BEST KNOWLEDGE OF (*NAME OF APPLICANT*), THERE ARE NO PATENTS THAT CLAIM THE LISTED DRUG REFERRED TO IN THIS ANDA~~APPLICATION~~ OR THAT CLAIM A USE OF THE LISTED DRUG.

(iii) *Method of use patent.* (A) If patent information is submitted under section 505(b) or (c) of the Federal Food, Drug, and Cosmetic Act ~~act~~ and § 314.53 for a patent claiming a method of using the listed drug, and the labeling for the drug product for which the applicant is seeking approval does not include an~~y~~ indication~~s~~ or other condition of use that ~~are~~ is covered by the method of use patent, a statement explaining that the method of use patent does not claim an~~y of the~~ proposed indication~~s~~ or other condition of use.

(B) If the labeling of the drug product for which the applicant is seeking approval includes an indication or other condition of use that, according to the patent information submitted under section 505(b) or (c) of the Federal Food, Drug, and Cosmetic Act ~~act~~ and § 314.53 or in the opinion of the applicant, is claimed by a method of use patent, an applicable certification under paragraph (a)(12)(i) of this section.

(iv) *Method of manufacturing patent.* An applicant is not required to make a certification with respect to any patent that claims only a method of manufacturing the listed drug.

(v) *Licensing agreements.* If the ~~abbreviated new drug application~~ANDA is for a drug or method of using a drug claimed by a patent and the applicant has a licensing agreement with the patent owner, ~~a certification under paragraph (a)(12)(i)(A)(*4*) of this section ("Paragraph IV Certification")~~ the applicant must submit a paragraph IV certification as to that patent

and a statement that the applicant ~~it~~ has been granted a patent license. If the patent owner consents to approval of the ANDA (if otherwise eligible for approval) as of a specific date, the ANDA must contain a written statement from the patent owner that it has a licensing agreement with the applicant and that it consents to approval of the ANDA as of a specific date

(vi) ~~*Late submission*~~*Untimely filing of patent information.* (A) If a patent on the listed drug is issued and the holder of the approved ~~application~~ NDA for the listed drug does not ~~submit~~ file with FDA the required information on the patent within 30 days of issuance of the patent, an applicant who submitted an ~~abbreviated new drug application~~ANDA for that drug that contained an appropriate patent certification or statement before the submission of the patent information is not required to submit a~~n amended certification~~ patent certification or statement to address the patent or patent information that is late-listed with respect to the pending ANDA. ~~An applicant whose abbreviated new drug application is submitted after a late submission of patent information, or whose pending abbreviated application was previously submitted but did not contain an appropriate patent certification at the time of the patent submission, shall submit a certification under paragraph (a)(12)(i) of this section or a statement under paragraph (a)(12)(iii) of this section as to that patent.~~ Except as provided in § 314.53(f)(1), an NDA holder's amendment to the description of the approved method(s) of use claimed by the patent will be considered untimely filing of patent information unless:

(1) The amendment to the description of the approved method(s) of use claimed by the patent is submitted within 30 days of patent issuance;

(2) The amendment to the description of the approved method(s) of use claimed by the patent is submitted within 30 days of approval of a corresponding change to product labeling; or

(3) The amendment to the description of the approved method(s) of use claimed by the patent is submitted within 30 days of a decision by the U.S. Patent and Trademark Office or by a Federal district court, the Court of Appeals for the Federal Circuit, or the U.S. Supreme Court that is specific to the patent and alters the construction of a method-of-use claim(s) of the patent, and the amendment contains a copy of the decision.

(B) An applicant whose ANDA is submitted after the NDA holder's untimely filing of patent information, or whose pending ANDA was previously submitted but did not contain an appropriate patent certification or statement at the time of the patent submission, must submit a certification under paragraph (a)(12)(i) of this section and/or a statement under paragraph (a)(12)(iii) of this section as to that patent.

(vii) *Disputed patent information.* If an applicant disputes the accuracy or relevance

of patent information submitted to FDA, the applicant may seek a confirmation of the correctness of the patent information in accordance with the procedures under § 314.53(f). Unless the patent information is withdrawn ~~or changed~~, the applicant ~~shall~~ must submit an appropriate certification or statement for each relevant patent.

(viii) *Amended certifications.* A patent certification or statement submitted under paragraphs (a)(12)(i) through ~~(a)(12)~~(iii) of this section may be amended at any time before the ~~effective date of the~~ approval of the ~~application~~ANDA. ~~However, an applicant who has submitted a paragraph IV patent certification may not change it to a paragraph III certification if a patent infringement suit has been filed against another paragraph IV applicant unless the agency has determined that no applicant is entitled to 180-day exclusivity or the patent expires before the lawsuit is resolved or expires after the suit is resolved but before the end of the 180-day exclusivity period.~~ If an applicant with a pending ~~application~~ ANDA voluntarily makes a patent certification for an untimely filed patent, the applicant may withdraw the patent certification for the untimely filed patent. An applicant ~~shall~~ must submit an amended certification ~~by letter or~~ as an amendment to a pending ~~application~~ ANDA~~or by letter to an approved application~~. Once an amendment ~~or letter~~ is submitted to change a certification, the ~~application~~ ANDA will no longer be considered to contain the prior certification.

(A) *After finding of infringement.* An applicant who has submitted a paragraph IV certification ~~under paragraph (a)(12)(i)(A)(4) of this section~~ and is sued for patent infringement ~~within 45 days of the receipt of notice sent under § 314.95 shall amend~~must submit an amendment to change its ~~the~~ certification if a court enters a ~~final judgment~~ decision from which no appeal has been or can be taken, or signs and enters a settlement order or consent decree in the action that includes a finding that the patent is infringed, unless the final decision, settlement order, or consent decree also finds the patent to be invalid~~in the action against the applicant is entered finding the patent to be infringed~~. In ~~the amended certification~~its amendment, the applicant ~~shall~~ must certify under paragraph (a)(12)(i)(A)(*3*) of this section that the patent will expire on a specific date, with respect to a patent claiming a method of use, the applicant may instead provide a statement under paragraph (a)(12)(ii) of this section the applicant amends its ANDA such that the applicant is no longer seeking approval for a method of use claimed by the patent. Once an amendment ~~or letter~~ for the change has been submitted, the ~~application~~ ANDA will no longer be considered to ~~be one containing~~contain a paragraph IV certification ~~under paragraph (a)(12)(i)(A)(4) of this section~~to the patent. If a final judgment finds the patent to be invalid and infringed, an amended certification is not required.

(B) *After ~~removal~~ request to remove~~of~~ a patent or patent information from the list.* If the list reflects that an NDA holder has

requested that a patent or patent information ~~is~~ be removed from the list and no ANDA applicant is eligible for 180-day exclusivity base on a paragraph IV certification to that patent, the patent or patent information will be removed and any applicant with a pending ~~application~~ ANDA (including a tentatively approved ~~application with a delayed effective date~~ANDA) who has made a certification with respect to such patent ~~shall amend~~must submit an amend to withdraw its certification. ~~The applicant shall certify under paragraph (a)(12)(ii) of this section that no patents described in paragraph (a)(12)(i) of this section claim the drug or, if other relevant patents claim the drug, shall amend the certification to refer only to those relevant patents.~~ In the amendment, the applicant ~~shall~~ must state the reason for ~~the change in~~withdrawing the certification or statement (that the patent ~~is or~~ has been removed from the list). If the list reflects that an NDA holder has requested that a patent or patent information be removed from the list and one or more first applicant are eligible for 180-day exclusivity based on a paragraph IV certification to that patent, the patent will remain listed until any 180-day exclusivity based on that patent has expire or has been extinguished. After any applicable 180-day exclusivity has expired or has been extinguished, the patent or patent information will be removed and any application with a pending ANDA (including a tentatively approved ANDA) who has made a certification with respect to such patent must submit an amendment to withdraw its certification. ~~A patent that is the subject of a lawsuit under § 314.107(c) shall not be removed from the list until FDA determines either that no delay in effective dates of approval is required under that section as a result of the lawsuit, that the patent has expired, or that any such period of delay in effective dates of approval is ended. An applicant shall submit an amended certification.~~ Once an amendment to withdraw the certification ~~or letter for the change~~ has been submitted, the ~~application~~ ANDA will no longer be considered to ~~be one containing~~to contain a paragraph IV certification ~~under paragraph (a)(12)(i)(A)(4) of this section~~to the patent. If removal of a patent from the list results in there being no patents listed for the listed drug identified in the ANDA, the applicant must submit an amended certification reflecting that there are no relevant patents.

(C) *Other amendments.* (*1*) Except as provided in paragraphs (a)(12)(vi) and (a)(12)(viii)(C)(*2*) of this section:~~,~~

(*i*) ~~a~~An applicant ~~shall~~ must amend a submitted certification or statement if, at any time before the ~~effective~~ date of the approval of the ~~application~~ANDA, the applicant learns that the submitted certification or statement is no longer accurate.

(ii) An applicant must submit an appropriate patent certification or statement under paragraph (a)(12)(i) and/or (iii) of this section if, after submission of the ANDA, a new patent is issued by the U.S. Patent and Trademark Office that, in the opinion of the applicant and to the best of its knowledge, claims the reference listed drug or that claims an approved use for such reference

listed drug and for which information is required to be filed under section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act and § 314.53. For a paragraph IV certification, the certification must not be submitted earlier than the first working day after the day the patent is published in the list.

(2) An applicant is not required to ~~amend~~ submit a supplement to change a submitted certification when information on a patent on the listed drug is submitted after the ~~effective date of~~ approval of the ~~abbreviated application~~ANDA.

(13) *Financial certification or disclosure statement.* An abbreviated application shall contain a financial certification or disclosure statement as required by part 54 of this chapter.

(b) *Drug products subject to the Drug Efficacy Study Implementation (DESI) review.* If the abbreviated new drug application is for a duplicate of a drug product that is subject to FDA's DESI review (a review of drug products approved as safe between 1938 and 1962) or other DESI-like review and the drug product evaluated in the review is a listed drug, the applicant shall comply with the provisions of paragraph (a) of this section.

(c) [Reserved]

(d) *Format of an ~~abbreviated application~~ANDA.* (1) The applicant must submit a complete archival copy of the ~~abbreviated application~~ANDA as required under paragraphs (a) and (c) of this section. FDA will maintain the archival copy during the review of the ~~application~~ ANDA to permit individual reviewers to refer to information that is not contained in their particular technical sections of the ~~application~~ANDA, to give other ~~agency~~ Agency personnel access to the ~~application~~ ANDA for official business, and to maintain in one place a complete copy of the ~~application~~ANDA.

(i) *Format of submission.* An applicant may submit portions of the archival copy of the abbreviated application in any form that the applicant and FDA agree is acceptable, except as provided in paragraph (d)(1)(ii) of this section.

(ii) *Labeling.* The content of labeling required under § 201.100(d)(3) of this chapter (commonly referred to as the package insert or professional labeling), including all text, tables, and figures, must be submitted to the agency in electronic format as described in paragraph (d)(1)(iii) of this section. This requirement applies to the content of labeling for the proposed drug product only and is in addition to the requirements of paragraph (a)(8)(ii) of this section that copies of the formatted label and all proposed labeling be submitted. Submissions under this paragraph must be made in accordance with part 11 of this chapter, except for the requirements of § 11.10(a), (c) through (h), and (k), and the corresponding requirements of § 11.30.

(iii) *Electronic format submissions.* Electronic format submissions

must be in a form that FDA can process, review, and archive. FDA will periodically issue guidance on how to provide the electronic submission (e.g., method of transmission, media, file formats, preparation and organization of files).

(2) For ~~abbreviated new drug applications~~ANDAs, the applicant ~~shall~~ must submit a review copy of the ~~abbreviated application~~ANDA that contains two separate sections. One section ~~shall~~ must contain the information described under paragraphs (a)(2) through ~~(a)~~(6), ~~(a)~~(8), and ~~(a)~~(9) of this section and section 505(j)(2)(A)(vii) of the ~~act~~ Federal Food, Drug, and Cosmetic Act and ~~one~~ a copy of the analytical procedures and descriptive information needed by FDA's laboratories to perform tests on samples of the proposed drug product and to validate the applicant's analytical procedures. The other section ~~shall~~ must contain the information described under paragraphs (a)(3), ~~(a)~~(7), and ~~(a)~~(8) of this section. Each of the sections in the review copy is required to contain a copy of the application form described under ~~§ 314.50(a)~~paragraph (a) of this section.

(3) [Reserved]

(4) The applicant may obtain from FDA sufficient folders to bind the archival, the review, and the field copies of the abbreviated application.

(5) The applicant shall submit a field copy of the abbreviated application that contains the technical section described in paragraph (a)(9) of this section, a copy of the application form required under paragraph (a)(1) of this section, and a certification that the field copy is a true copy of the technical section described in paragraph (a)(9) of this section contained in the archival and review copies of the abbreviated application.

21 C.F.R. § 314.95 – NOTICE OF CERTIFICATION OF INVALIDITY, UENFORCEABILITY OR NONINFRINGEMENT OF A PATENT

(a) *Notice of certification.* For each patent that claims the listed drug or that claims a use for such listed drug for which the applicant is seeking approval and for which the applicant submits a paragraph IV certification, ~~that the applicant certifies under § 314.94(a)(12) is invalid, unenforceable, or will not be infringed,~~ the applicant ~~shall~~ must send notice of such certification by registered or certified mail, return receipt requested, or by a designated delivery service, as defined in paragraph (g) of this section to each of the following persons:

(1) Each owner of the patent ~~which~~ that is the subject of the certification or the representative designated by the owner to

receive the notice. The name and address of the patent owner or its representative may be obtained from the United States Patent and Trademark Office; and

(2) The holder of the approved ~~application~~ NDA under section 505(b) of the Federal Food, Drug, and Cosmetic Act ~~act~~ for the listed drug that is claimed by the patent and for which the applicant is seeking approval, or, if the ~~application~~ NDA holder does not reside or maintain a place of business within the United States, the ~~application~~ NDA holder's attorney, agent, or other authorized official. The name and address of the ~~application~~ NDA holder or its attorney, agent, or authorized official may be obtained ~~from~~ by sending a written or electronic communication to the Orange Book Staff, Office of Generic Drugs, ~~7500~~ 7620 Standish Pl., Rockville, MD 20855 or to the Orange Book Staff as the email address listed on the Agency's Web site at http://www.fda.gov.

(3) This paragraph (a) does not apply to a method of use patent that does not claim a use ~~claims no uses~~ for which the applicant is seeking approval.

(4) An applicant may send notice by an alternative method only if FDA has agreed in advance that the method will produce an acceptable form of documentation.

(b) *Sending the notice.* (1) Except as provided under paragraph (d) of this section, ~~T~~the applicant ~~shall~~ must send the notice required by paragraph (a) of this section on or after the date ~~when~~ it receives a paragraph IV acknowledgment letter from ~~FDA~~FDA, ~~an acknowledgment letter stating that its abbreviated new drug application is sufficiently complete to permit a substantive review.~~ but not later than 20 days after the date of the postmark on the paragraph IV acknowledgment letter. The 20-day clock described in this paragraph (b) begins on the day after the date of the postmark on the paragraph IV acknowledgment letter. When the 20th day falls on Saturday, Sunday, or a Federal holiday, the 20th day will be the next day that is not a Saturday, Sunday, or Federal holiday.

~~At the same time, the applicant shall amend its abbreviated new drug application to include a statement certifying that the notice has been provided to each person identified under paragraph (a) of this section and that the notice met the content requirements under paragraph (c) of this section.~~

(2) Any notice required by paragraph (a) of this section is invalid if it is sent before the applicant's receipt of a paragraph IV acknowledgment letter, or before the first working day after the day the patent is published in the list. The applicant will not have complied with this paragraph (b) until it sends valid notice.

(3) The applicant must submit to FDA an amendment to its ANDA that includes a statement certifying that the notice has been provided to each person identified under paragraph 261 (a) of this section and that the notice met the content requirements under paragraph (c) of this section. A copy of the

notice itself need not be submitted to the Agency.

(c) *Contents of a notice.* In the notice, the applicant ~~shall~~ must cite section 505(j)(2)(B)(~~ii~~iv) of the Federal Food, Drug, and Cosmetic Act ~~act~~ and ~~shall~~ the notice must include, but is not ~~be~~ limited to, the following information:

(1) A statement that FDA has received an ~~abbreviated new drug application~~ANDA submitted by the applicant containing any required bioavailability or bioequivalence data or information.

(2) The ~~abbreviated application~~ANDA number.

(3) A statement that the applicant has received the paragraph IV acknowledgment letter for the ANDA.

(4) The established name, if any, as defined in section 502(e)(3) of the Federal Food, Drug, and Cosmetic Act~~act~~, of the proposed drug product.

(~~4~~5) The active ingredient, strength, and dosage form of the proposed drug product.

(~~5~~6) The patent number and expiration date~~, as submitted to the agency or as known to the applicant,~~ of each listed patent for the reference listed drug alleged to be invalid, unenforceable, or not infringed.

(~~6~~7) A detailed statement of the factual and legal basis of the applicant's opinion that the patent is not valid, unenforceable, or will not be infringed. The applicant ~~shall~~ must include in the detailed statement:

(i) For each claim of a patent alleged not to be infringed, a full and detailed explanation of why the claim is not infringed.

(ii) For each claim of a patent alleged ~~not~~ to be ~~invalid or unenforceable~~infringed invalid or unenforceable, a full and detailed explanation of ~~the grounds supporting the allegation~~why the claim is not infringed the grounds supporting the allegation.

(8) If the applicant alleges that the patent will not be infringed and the applicant seeks to preserve the option to later file a civil action for declaratory judgment in accordance with section 505(j)(5)(C) of the Federal Food, Drug, and Cosmetic Act, then the notice must be accompanied by an offer of confidential access to the ANDA for the sole and limited purpose of evaluating possible infringement of the patent that is the subject of the paragraph IV certification.

(~~7~~9) If the applicant does not reside or have a place of business in the United States, the name and address of an agent in the United States authorized to accept service of process for the applicant.

(d) *Amendment or supplement to an ~~abbreviated application~~ANDA.* (1) If, after receipt of a paragraph IV acknowledgment letter or acknowledgment letter, an applicant submits an amendment or supplement to its ~~abbreviated application is amended to include the certification described in~~

~~§ 314.94(a)(12)(i)(A)(4),~~ ANDA that includes a paragraph IV certification, the applicant ~~shall~~ must send the notice required by paragraph (a) of this section at the same time that the amendment or supplement to the ~~abbreviated application~~ANDA is submitted to ~~FDA~~FDA, regardless of whether the applicant has already given notice with respect to another such certification contained in the ANDA or in an amendment or supplement to the ANDA.

(2) If, before receipt of a paragraph IV acknowledgment letter, an applicant submits an amendment to its ANDA that includes a paragraph IV certification, the applicant must send the notice required by paragraph (a) of this section in accordance with the procedures in paragraph (b) of this section. If an ANDA applicant's notice of its paragraph IV certification is timely provided in accordance with paragraph (b) of this section and the applicant has not submitted a previous paragraph IV certification, FDA will base its determination of whether the applicant is a first applicant on the date of submission of the amendment containing the paragraph IV certification.

(3) An applicant that submits an amendment or supplement to seek approval of a different strength must provide notice of any paragraph IV certification in accordance with paragraph (d)(1) or (2) of this section, as applicable.

(e) *Documentation of timely sending and ~~of~~ receipt of notice.* The applicant ~~shall~~ must amend its ~~abbreviated application~~ANDA to provide documentation of the date of receipt ~~document receipt~~ of the notice required under paragraph (a) of this section by each person provided the notice. The amendment must be submitted to FDA within 30 days after the last date on which notice was received by a person described in paragraph (a) of this section. The applicant's amendment ~~shall~~ also must documentation that its notice was sent on a date that complies with the timeframe required by paragraph (b) or (d) of this section, as applicable, and a dated and a dated printout of the entry for the reference listed drug in FDA's "Approved Drug Products With Therapeutic Equivalence Evaluations" (the list) that includes the patent that is the subject of the paragraph IV certification. ~~include a copy of the return receipt or other similar evidence of the date the notification was received.~~ FDA will accept, as adequate documentation of the date the notice was sent, a copy of the registered mail receipt, certified mail receipt, or receipt from a designated delivery service as defined in paragraph (g) of this section. FDA will accept as adequate documentation of the date of receipt a return receipt, signature proof of delivery by a designated delivery service, or a letter acknowledging receipt by the person provided the notice.~~of receipt a return receipt or a letter acknowledging receipt by the person provided the notice.~~ An applicant may rely on another form of documentation only if FDA has agreed to such documentation in advance. A copy of the notice itself need not be submitted to the ~~agency~~Agency.

(f) ~~*Approval*~~*Forty-five day period after receipt of notice*. If the requirements of this

section are met, FDA will presume the notice to be complete and sufficient, and it will count the day following the date of receipt of the notice by the patent owner or its representative and by the approved ~~application~~ NDA holder or its attorney, agent, or other authorized official as the first day of the 45-day period provided for in section 505(j)(~~4~~5)(B)(iii) of the ~~act~~Federal Food, Drug, and Cosmetic Act. FDA may, if the applicant provides a written statement to FDA that a later date should be used, count from such later date.

(g) Designated delivery services. (1) For purposes of this section, the term "designated delivery service" means any delivery service provided by a trade or business that the Agency determines:

(i) Is available to the general public throughout the United States;

(ii) Records electronically to its database, kept in the regular course of its business, or marks on the cover in which any item referred to in this section is to be delivered, the date on which such item was given to such trade or business for delivery; and (iii) Provides overnight or 2-day delivery service throughout the United States.

(2) FDA may periodically issue guidance regarding designated delivery services.

21 C.F.R. § 314.96 – AMENDMENTS TO AN UNAPPROVED ~~ABBREVIATED APPLICATION~~ANDA

(a) *Abbreviated new drug application.* (1) An applicant may amend an abbreviated new drug application that is submitted under § 314.94, but not yet approved, to revise existing information or provide additional information. Amendments containing bioequivalence studies must contain reports of all bioequivalence studies conducted by the applicant on the same drug product formulation, unless the information has previously been submitted to FDA in the abbreviated new drug application. A complete study report must be submitted for any bioequivalence study upon which the applicant relies for approval. For all other bioequivalence studies conducted on the same drug product formulation as defined in § 320.1(g) of this chapter, the applicant must submit either a complete or summary report. If a summary report of a bioequivalence study is submitted and FDA determines that there may be bioequivalence issues or concerns with the product, FDA may require that the applicant submit a complete report of the bioequivalence study to FDA.

(2) Submission of an amendment containing significant data or information before the end of the initial review cycle

constitutes an agreement between FDA and the applicant to extend the initial review cycle only for the time necessary to review the significant data or information and for no more than 180 days.

(b) *Field copy.* The applicant shall submit a field copy of each amendment to § 314.94(a)(9). The applicant, other than a foreign applicant, shall include in its submission of each such amendment to FDA a statement certifying that a field copy of the amendment has been sent to the applicant's home FDA district office.

(c) *Different listed drug.* An applicant may not amend an ANDA to seek approval of a drug referring to a listed drug that is different from the reference listed drug identified in the ANDA. This paragraph (c) applies if, at any time before the approval of the ANDA, a different listed drug is approved that is the pharmaceutical equivalent to the product in the ANDA and is designated as a reference listed drug. This paragraph (c) also applies if changes are proposed in an amendment to the ANDA such that the proposed product is a pharmaceutical equivalent to a different listed drug than the reference listed drug identified in the ANDA. A change of the reference listed drug must be submitted in a new ANDA. However, notwithstanding the limitation described in this paragraph (c), an applicant may amend the ANDA to seek approval of a different strength.

(d)(1) *Patent certification requirements.* An amendment to an ANDA is required to contain an appropriate patent certification or statement described in § 314.94(a)(12) or a recertification for a previously submitted paragraph IV certification if approval is sought for any of the following types of amendments:

(i) To add a new indication or other condition of use;

(ii) To add a new strength;

(iii) To make other than minor changes in product formulation; or

(iv) To change the physical form or crystalline structure of the active ingredient.

(2) If the amendment to the ANDA does not contain a patent certification or statement, the applicant must verify that the proposed change described in the amendment is not one of the types of amendments described in paragraph (d)(1) of this section.

21 C.F.R. § 314.97 – SUPPLEMENTS AND OTHER CHANGES TO AN APPROVED ~~ABBREVIATED APPLICATION~~ANDA

(a) *General requirements.* The applicant ~~shall~~ must comply with the requirements of §§ 314.70 and 314.71 regarding the submission of supplemental ~~applications~~

ANDAs and other changes to an approved ~~abbreviated application~~ANDA.

(b) Different listed drug. An applicant may not supplement an ANDA to seek approval of a drug referring to a listed drug that is different from the current reference listed drug identified in the ANDA. This paragraph (b) applies if changes are proposed in a supplement to the ANDA such that the proposed product is a pharmaceutical equivalent to a different listed drug than the reference listed drug identified in the ANDA. A change of reference listed drug must be submitted in a new ANDA. However, notwithstanding the limitation described in this paragraph (b), an applicant may supplement the ANDA to seek approval of a different strength.

21 C.F.R. § 314.99 – OTHER RESPONSIBILITIES OF AN APPLICANT OF AN ~~ABBREVIATED APPLICATION~~ANDA

(a) An applicant ~~shall msut~~ must comply with the requirements of § 314.65 regarding withdrawal by the applicant of an unapproved ~~abbreviated application~~ANDA and § 314.72 regarding a change in ownership of an ~~abbreviated application~~ANAD~~D~~ANDA.

(b) An applicant may ask FDA to waive under this section any requirement that applies to the applicant under §§ 314.92 through 314.99. The applicant ~~shall msut~~must comply with the requirements for a waiver under § 314.90. If FDA grants the applicant's waiver request with respect to a requirement under §§ 314.92 through 314.99, the waived requirement will not constitute a basis for refusal to approve an ANDA under § 314.127.

21 C.F.R. § 314.101 – FILING AN ~~APPLICATION~~ NDA AND RECEIVING AN ~~ABBREVIATED NEW DRUG APPLICATION~~ANDA

(a)(1) *Filing an NDA.* Within 60 days after FDA receives an ~~application~~NDA, the ~~agency~~ Agency will determine whether the ~~application~~ NDA may be filed. The filing of an ~~application~~ NDA means that FDA has made a threshold determination that the ~~application~~ NDA is sufficiently complete to permit a substantive review.

(2) If FDA finds that none of the reasons in paragraphs (d) and (e) of this section for refusing to file the ~~application~~ NDA apply, the ~~agency~~ Agency will file the ~~application~~

NDA and notify the applicant in writing. In the case of a 505(b)(2) application that contains a paragraph IV certification, the applicant will be notified via a paragraph IV acknowledgment letter. The date of filing will be the date 60 days after the date FDA received the ~~application~~NDA. The date of filing begins the 180-day period described in section 505(c) of the ~~act~~Federal Food, Drug, and Cosmetic Act. This 180-day period is called the "filing clock."

(3) If FDA refuses to file the ~~application~~NDA, the ~~agency~~ Agency will notify the applicant in writing and state the reason under paragraph (d) or (e) of this section for the refusal. If FDA refuses to file the ~~application~~ NDA under paragraph (d) of this section, the applicant may request in writing within 30 days of the date of the ~~agency's~~ Agency's notification an informal conference with the ~~agency~~ Agency about whether the ~~agency~~ Agency should file the ~~application~~NDA. If, following the informal conference, the applicant requests that FDA file the ~~application~~ NDA (with or without amendments to correct the deficiencies), the ~~agency~~ Agency will file the ~~application~~ NDA over protest under paragraph (a)(2) of this section, notify the applicant in writing, and review it as filed. If the ~~application~~ NDA is filed over protest, the date of filing will be the date 60 days after the date the applicant requested the informal conference. The applicant need not resubmit a copy of an ~~application~~ NDA that is filed over protest. If FDA refuses to file the ~~application~~ NDA under paragraph (e) of this section, the applicant may amend the ~~application~~ NDA and resubmit it, and the ~~agency~~ Agency will make a determination under this section whether it may be filed.

(b)(1) *Receiving an ANDA.* An ~~abbreviated new drug application~~ANDA will be reviewed after it is submitted to determine whether the ANDA~~abbreviated application~~ may be received. Receipt of an ANDA ~~abbreviated new drug application~~ means that FDA has made a threshold determination that the abbreviated application is ~~sufficiently complete to permit a substantive review~~substantially complete.

(2) If FDA finds that none of the reasons in paragraphs (d) and (e) of this section for considering the ANDA ~~abbreviated new drug application~~ not to have been received applies, the ANDA is substantially complete and the ~~agency~~ Agency will receive the ANDA ~~abbreviated new drug application~~ and notify the applicant in writing. If FDA determines, upon evaluation, that an ANDA was substantially complete as of the date it was submitted to FDA, FDA will consider the ANDA to have been received as of the date of submission. In the case of an ANDA that contains a paragraph IV certification, the applicant will be notified via a paragraph IV acknowledgment letter.

(3) If FDA considers the ~~abbreviated new drug application~~ANDA not to have been received under paragraph (d) or (e) of this section, FDA will notify the applicant of the refuse-to-receive decision.~~, ordinarily by telephone.~~ The applicant may then:

(i) Withdraw the ANDA~~abbreviated new drug application~~ under § 314.99; or

(ii) ~~Amend the abbreviated new drug application to correct the deficiencies~~Correct the deficiencies and resubmit the ANDA; or

(iii) Take no action, in which case FDA may consider the ANDA withdrawn after 1 year.~~will refuse to receive the abbreviated new drug application.~~

(c) [Reserved]

(d) *NDA or ANDA deficiencies.* FDA may refuse to file an ~~application~~ NDA or may not consider an ANDA ~~abbreviated new drug application~~ to be received if any of the following applies:

(1) The ~~application~~ NDA or ANDA does not contain a completed application form.

(2) The ~~application~~ NDA or ANDA is not submitted in the form required under § 314.50 or § 314.94.

(3) The ~~application or abbreviated application~~NDA or ANDA is incomplete because it does not on its face contain information required under section 505(b), section 505(j)~~, or section 507~~ of the ~~act~~ Federal Food, Drug, and Cosmetic Act and § 314.50 or § 314.94. In determining whether an ANDA is incomplete on its face, FDA will consider the nature (e.g., major or minor) of the deficiencies, including the number of deficiencies in the ANDA.

(4) The applicant fails to submit a complete environmental assessment, which addresses each of the items specified in the applicable format under § 25.40 of this chapter or fails to provide sufficient information to establish that the requested action is subject to categorical exclusion under § 25.30 or § 25.31 of this chapter.

(5) The ~~application or abbreviated application~~NDA or ANDA does not contain an accurate and complete English translation of each part of the NDA or ANDA ~~application~~ that is not in English.

(6) The NDA or ANDA ~~application~~ does not contain a statement for each nonclinical laboratory study that ~~it~~ the study was conducted in compliance with the requirements set forth in part 58 of this chapter, or, for each study not conducted in compliance with part 58 of this chapter, a brief statement of the reason for the noncompliance.

(7) The NDA or ANDA ~~application~~ does not contain a statement for each clinical study that ~~it~~ the study was conducted in compliance with the institutional review board regulations in part 56 of this chapter, or was not subject to those regulations, and that it was conducted in compliance with the informed consent regulations in part 50 of this chapter, or, if the study was subject to but was not conducted in compliance with those regulations, the NDA or ANDA ~~application~~ does not contain a brief statement of the reason for the noncompliance.

(8) The drug product that is the subject of the submission is already covered by an approved NDA or ANDA~~application or~~

~~abbreviated application~~ and the applicant of the submission:

(i) Has an approved application or abbreviated application NDA or ANDA for the same drug product; or

(ii) Is merely a distributor and/or repackager of the already approved drug product.

(9) The ~~application~~ NDA is submitted as a 505(b)(2) application for a drug that is a duplicate of a listed drug and is eligible for approval under section 505(j) of the Federal Food, Drug, and Cosmetic Act~~act~~.

(e) *Regulatory deficiencies.* The ~~agency~~ Agency will refuse to file an ~~application~~ NDA or will consider an ~~abbreviated new drug application~~ANDA not to have been received if any of the following applies:

(1) The drug product is subject to licensing by FDA under the Public Health Service Act (42 U.S.C. 201 *et seq.*) and subchapter F of this chapter.

(2) ~~In the case~~Submission of a 505(b)(2) application or an ~~abbreviated new drug application~~ANDA is not permitted under section 505(c)(3)(E)(ii), 505(j)(5)(F)(ii), 505A(b)(1)(A)(i)(I), 505A(c)(1)(A)(i)(I), or 505E(a) of the Federal Food, Drug, and Cosmetic Act. ~~, the drug product contains the same active moiety as a drug that:~~

~~(i) Was approved after September 24, 1984, in an application under section 505(b) of the act, and~~

~~(ii) Is entitled to a 5-year period of exclusivity under section 505(c)(3)(D)(ii) and (j)(4)(D)(ii) of the act and § 314.108(b)(2), unless the 5-year exclusivity period has elapsed or unless 4 years of the 5-year period have elapsed and the application or abbreviated application contains a certification of patent invalidity or noninfringement described in § 314.50(i)(1)(i)(A)(*4*) or § 314.94(a)(12)(i)(A)(*4*).~~

(f)(1) *Outcome of FDA review.* Within 180 days after the date of filing, plus the period of time the review period was extended (if any), FDA will either:

(i) Approve the ~~application~~NDA; or

(ii) Issue a notice of opportunity for a hearing if the applicant asked FDA to provide it an opportunity for a hearing on an ~~application~~ NDA in response to a complete response letter.

(2) Within 180 days after the date of receipt, plus the period of time the review clock was extended (if any), FDA will either approve or disapprove the ~~abbreviated new drug application~~ANDA. If FDA disapproves the ~~abbreviated new drug application~~ANDA, FDA will issue a notice of opportunity for hearing if the applicant asked FDA to provide it an opportunity for a hearing on an ~~abbreviated new drug application~~ANDA in response to a complete response letter.

(3) This paragraph (f) does not apply to ~~applications or abbreviated~~

~~applications~~NDAs or ANDAs that have been withdrawn from FDA review by the applicant.

21 C.F.R. § 314.105 – APPROVAL OF AN ~~APPLICATION~~ NDA AND AN ~~ABBREVIATED APPLICATION~~ ANDA

(a) ~~The Food and Drug Administration~~FDA will approve an ~~application~~ NDA and send the applicant an approval letter if none of the reasons in § 314.125 for refusing to approve the ~~application~~ NDA applies. ~~An approval becomes effective on the date of the issuance of the approval letter, except with regard to an approval under section 505(b)(2) of the act with a delayed effective date. An approval with a delayed effective date is tentative and does not become final until the effective date. A new drug product or antibiotic approved under this paragraph may not be marketed until an approval is effective.~~ FDA will issue a tentative approval letter if an NDA 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 the listed drug under section 527 of the Federal Food, Drug, and Cosmetic Act and § 316.31 of this chapter, or if a 505(b)(2) application 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)(3) 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; or because there is a period of exclusivity for the listed drug under section 505E of the Federal Food, Drug, and Cosmetic Act. A drug product that is granted tentative approval is not an approved drug and will not be approved until FDA issues an approval after any necessary additional review of the NDA. FDA's tentative approval of a drug product is based on information available to FDA at the time of the tentative approval letter (i.e., information in the 505(b)(2) application and the status of current good manufacturing practices of the facilities used in the manufacturing and testing of the drug product) and is therefore subject to change on the basis of new information that may come to FDA's attention. A new drug product may not be marketed until the date of approval.

(b) FDA will approve an ~~application~~ NDA and issue the applicant an approval letter on the basis of draft labeling if the only deficiencies in the ~~application~~ NDA concern editorial or similar minor deficiencies in the draft labeling. Such approval will be conditioned upon the applicant incorporating the specified labeling changes exactly as directed, and upon the applicant submitting to FDA a

copy of the final printed labeling prior to marketing.

(c) FDA will approve an ~~application~~ NDA after it determines that the drug meets the statutory standards for safety and effectiveness, manufacturing and controls, and labeling, and an ~~abbreviated application~~ANDA after it determines that the drug meets the statutory standards for manufacturing and controls, labeling, and, where applicable, bioequivalence. While the statutory standards apply to all drugs, the many kinds of drugs that are subject to the statutory standards and the wide range of uses for those drugs demand flexibility in applying the standards. Thus FDA is required to exercise its scientific judgment to determine the kind and quantity of data and information an applicant is required to provide for a particular drug to meet the statutory standards. FDA makes its views on drug products and classes of drugs available through guidance documents, recommendations, and other statements of policy.

(d) FDA will approve ~~an abbreviated new drug application~~ANDA and send the applicant an approval letter if none of the reasons in § 314.127 for refusing to approve the ~~abbreviated new drug application~~ANDA applies. ~~The approval becomes effective on the date of the issuance of the agency's approval letter unless the approval letter provides for a delayed effective date. An approval with a delayed effective date is tentative and does not become final until the effective date. A new drug product approved under this paragraph may not be introduced or delivered for introduction into interstate commerce until approval of the abbreviated new drug application is effective. Ordinarily, the effective date of approval will be stated in the approval letter.~~ FDA will issue a tentative approval letter if an 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 the listed drug under section 527 of the Federal Food, Drug, and Cosmetic Act and § 316.31 of this chapter, or cannot be approved until the conditions in § 314.107(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; or because there is a period of exclusivity for the listed drug under section 505E of the Federal Food, Drug, and Cosmetic Act. A drug product that is granted tentative approval is not an approved drug and will not be approved until FDA issues an approval after any necessary additional review of the ANDA. FDA's tentative approval of a drug product is based on information available to FDA at the time of the tentative approval letter (i.e., information in the ANDA and the status of current good manufacturing practices of the facilities used in the manufacturing and testing of the drug product) and is therefore subject to change on the basis of new information that may come to FDA's attention. A new drug product may not be marketed until the date of approval.

21 C.F.R. § 314.107 – ~~EFFECTIVE~~ DATE OF APPROVAL OF A 505(b)(2) APPLICATION OR ~~ABBREVIATED NEW DRUG APPLICATION UNDER SECTION 505(j) OF THE ACT~~ANDA

(a) *General.* A drug product may be introduced or delivered for introduction into interstate commerce when the 505(b)(2) application or ANDA ~~approval of the application or abbreviated application~~ for the drug product ~~becomes effective~~is approved. ~~Except as provided in this section, approval of an application or abbreviated application for a drug product becomes effective on the date~~ A 505(b)(2) application or ANDA for a drug product is approved on the date FDA issues an approval letter under § 314.105 for 505(b)(2) application or ANDA~~the application or abbreviated application~~.

(b) *Effect of patent(s) on the listed drug.* As described in paragraphs (b)(1) and (2) of this section, the status of patents listed for the listed drug(s) relied upon or reference listed drug, as applicable, must be considered in determining the first possible date on which a 505(b)(2) application or ANDA can be approved. The criteria in paragraphs (b)(1) and (2) of this section will be used to determine, for each relevant patent, the date that patent will no longer prevent approval. The first possible date on which the 505(b)(2) application or ANDA can be approved will be calculated for each patent, and the 505(b)(2) application or ANDA may be approved on the last applicable date.~~If approval of an abbreviated new drug application submitted under section 505(j) of the act or of a 505(b)(2) application is granted, that approval will become effective in accordance with the following:~~

(1) *Timing of approval based on patent certification or statement.* If none of the reasons in § 314.125 or § 314.127, as applicable, for refusing to approve the 505(b)(2) application or ANDA applies, and none of the reasons in paragraph (d) of this section for delaying approval applies, the 505(b)(2) application or ANDA may be approved as follows: ~~*Date of approval letter.* Except as provided in paragraphs (b)(3), (b)(4), and (c) of this section, approval will become effective on the date FDA issues an approval letter under § 314.105 if the applicant certifies under § 314.50(i) or § 314.94(a)(12) that:~~

(i) Immediately, if the applicant certifies under § 314.50(i) or § 314.94(a)(12) that:

~~(i) There are no relevant patents; or~~

(~~ii~~A) The applicant is aware of a relevant patent but the patent information required under section 505 (b) or (c) of the ~~act~~ Federal Food, Drug, and Cosmetic Act has not been submitted to FDA; or

(~~iii~~B) The relevant patent has expired; or

(~~iv~~C) The relevant patent is invalid, unenforceable, or will not be infringed except as provided in paragraphs (b)(3) and (c) of this section, and the 45-day period provided for in section 505(c)(3)(C) and (j)(5)(B)(iii) of the Federal Food, Drug, and Cosmetic Act has expired; or

(D) There are no relevant patents.

~~.~~ (ii) Immediately, if the applicant submits an appropriate statement under § 314.50(i) or § 314.94(a)(12) explaining that a method-of-use patent does not claim an indication or other condition of use for which the applicant is seeking approval, except that if the applicant also submits a paragraph IV certification to the patent, then the 505(b)(2) application or ANDA may be approved as provided in paragraph (b)(1)(i)(C) of this section.

(iii) On the date specified, if the applicant certifies under § 314.50(i) or § 314.94(a)(12) that the relevant patent will expire on a specified date.

(2) Patent information filed after submission of 505(b)(2) application or ANDA. If the holder of the approved NDA for the listed drug submits patent information required under § 314.53 after the date on which the 505(b)(2) application or ANDA was submitted to FDA, the 505(b)(2) applicant or ANDA applicant must comply with the requirements of § 314.50(i)(4) and (6) and § 314.94(a)(12)(vi) and (viii) regarding submission of an appropriate patent certification or statement. If the applicant submits an amendment certifying under § 314.50(i)(1)(i)(A)(4) or § 314.94(a)(12)(i)(A)(4) that the relevant patent is invalid, unenforceable, or will not be infringed, and complies with the requirements of § 314.52 or § 314.95, the 505(b)(2) application or ANDA may be approved immediately upon submission of documentation of receipt of notice of paragraph IV certification under § 314.52(e) or § 314.95(e). The 45-day period provided for in section 505(c)(3)(C) and (j)(5)(B)(iii) of the Federal Food, Drug, and Cosmetic Act does not apply in these circumstances. ~~(2) *Patent expiration.* If the applicant certifies under § 314.50(i) or § 314.94(a)(12) that the relevant patent will expire on a specified date, approval will become effective on the specified date.~~

(3) *Disposition of patent litigation.* (i) *Approval upon expiration of 30-month period or 7½ years from date of listed drug approval.* ~~(A~~A~~)~~ Except as provided in paragraphs (b)(3)(ii~~), (b)(3)(iii), and (b)(3)(iv)~~ through (viii) of this section, if, with respect to patents for which required information was submitted under § 314.53 before the date on which the 505(b)(2) application or ANDA was submitted to FDA (excluding an amendment or supplement to the 505(b)(2) application or ANDA), the applicant certifies under § 314.50(i) or § 314.94(a)(12) that the relevant patent is invalid, unenforceable, or will not be infringed, and the patent owner or its representative or the exclusive patent licensee brings suit for patent infringement within 45 days of receipt ~~by the patent owner~~ of the notice of certification from the applicant under § 314.52 or § 314.95, the

505(b)(2) application or ANDA may be approved~~approval may be made effective~~ 30 months after the later of the date of the receipt of the notice of certification by ~~the~~ any owner of the listed patent ~~patent owner or by the exclusive licensee~~ or by the NDA hold~~l~~er (or their representative(s)) unless the court has extended or reduced the period because of a failure of either the plaintiff or defendant to cooperate reasonably in expediting the action; or

(B) If the patented drug product qualifies for 5 years of exclusive marketing under § 314.108(b)(2) and the patent owner or its representative or the exclusive patent licensee brings suit for patent infringement during the 1-year period beginning 4 years after the date ~~the patented drug was approved~~of approval of the patented drug and within 45 days of receipt ~~by the patent owner~~ -of the notice of certification from the applicant under § 314.52 or § 314.95, the 505(b)(2) application or ANDA ~~the approval~~ may be approved~~made effective~~ at the expiration of the 7~~1/2~~½ years from the date of approval of the ~~application~~ NDA for the patented drug product.

(ii) *Federal district court decision of invalidity, unenforceability or non-infringement.* If before the expiration of the 30-month period, or 7~~1/2~~½ -years where applicable, the district court ~~issues a final order~~decides that the patent is invalid, unenforceable, or not infringed (including any substantive determination that there is no cause of action for patent infringement or invalidity), the 505(b)(2) application or ANDA may be approved on~~, approval may be made effective on the date the court enters judgment;~~

(A) The date on which the court enters judgment reflecting the decision; or

(B) The date of a settlement order or consent decree signed and entered by the court stating that the patent that is the subject of the certification is invalid, unenforceable, or not infringed.

(iii) *Appeal of Federal district court judgment of infringement.* If before the expiration of the 30-month period, or 7~~1/2~~½ years where applicable, the district court ~~issues a final order or judgment~~decides that the patent has been infringed, and if the judgment of the district court is appealed, the 505(b)(2) application or ANDA may be approved on:

(A) The date on which the mandate is issued by the court of appeals entering judgment that the patent is invalid, unenforceable, or not infringed (including any substantive determination that there is no cause of action for patent infringement or invalidity); or

(B) The date of a settlement order or consent decree signed and entered by the court of appeals stating that the patent that is the subject of the certification is invalid, unenforceable, or not infringed. ~~approval may be made effective on the date the court determines that the patent will expire or otherwise orders; or~~

(iv) *Affirmation or non-appeal of Federal district court judgment of infringement.* If before the expiration of the 30-month period, or 7½ years where applicable, the district court decides that the patent has been infringed, and if the judgment of the district court is not appealed or is affirmed, the 505(b)(2) application or ANDA may be approved no earlier than the date specified by the district court in an order under 35 U.S.C. 271(e)(4)(A).

(~~iv~~v) *Grant of preliminary injunction by Federal district court.* If before the expiration of the 30-month period, or 7~~1/2~~ ½ years where applicable, the district court grants a preliminary injunction prohibiting the applicant from engaging in the commercial manufacture or sale of the drug product until the court decides the issues of patent validity and infringement, and if the court later decides that: ~~the patent is invalid, unenforceable, or not infringed, approval may be made effective on the date the court enters a final order or judgment that the patent is invalid, unenforceable, or not infringed.~~

(A) The patent is invalid, unenforceable, or not infringed, the 505(b)(2) application or ANDA may be approved as provided in paragraph (b)(3)(ii) of this section; or

(B) The patent is infringed, the 505(b)(2) application or ANDA may be approved as provided in paragraph (b)(3)(iii) or (iv) of this section, whichever is applicable.

(vi) Written consent to approval by patent owner or exclusive patent licensee. If before the expiration of the 30-month period, or 7½ years where applicable, the patent owner or the exclusive patent licensee (or their representatives) agrees in writing that the 505(b)(2) application or ANDA may be approved any time on or after the date of the consent, approval may be granted on or after that date.

(vii) Court order terminating 30-month or 7½-year period. If before the expiration of the 30-month period, or 7½ years where applicable, the court enters an order requiring the 30-month or 7½-year period to be terminated, the 505(b)(2) application or ANDA may be approved in accordance with the court's order.

(viii) Court order of dismissal without a finding of infringement. If before the expiration of the 30-month period, or 7½ years where applicable, the court(s) enter(s) an order of dismissal, with or without prejudice, without a finding of infringement in each pending suit for patent infringement brought within 45 days of receipt of the notice of paragraph IV certification sent by the 505(b)(2) or ANDA applicant, the 505(b)(2) application or ANDA may be approved on or after the date of the order.

(~~v~~4) *Tentative approval.* FDA will issue a tentative approval letter when tentative approval is appropriate in accordance with ~~paragraph (b)(3) of~~ this section. In order for 505(b)(2) application or ANDA to be approved ~~an approval to be made effective~~ under paragraph (b)(3) of this section, the applicant must receive an approval letter from the ~~agency~~ Agency. ~~indicating that the~~

~~application has received final approval.~~ Tentative approval of an ~~application~~ NDA or ANDA does not constitute "approval" of an ~~application~~ NDA or ANDA and cannot, absent ~~a final~~an approval letter from the ~~agency~~Agency, result in an ~~effective~~ approval under paragraph (b)(3) of this section.

~~(4) *Multiple certifications.* If the applicant has submitted certifications under § 314.50(i) or § 314.94(a)(12) for more than one patent, the date of approval will be calculated for each certification, and the approval will become effective on the last applicable date.~~

(c) ~~*Subsequent abbreviated new drug application submission*~~*Timing of approval of subsequent ANDA*. (1) If an ~~abbreviated new drug application~~ANDA contains a paragraph IV certification ~~that~~ for a relevant patent and the ANDA is not that of a first applicant, the ANDA is regarded as the ANDA of a subsequent applicant. The ANDA of a subsequent applicant will not be approved during the period when any first applicant is eligible for 180-day exclusivity or during the 180-day exclusivity period of a first applicant. Any applicable 180-day exclusivity period cannot extend beyond the expiration of the patent upon which the 180-day exclusivity period was based. ~~is invalid, unenforceable, or will not be infringed and the application is for a generic copy of the same listed drug for which one or more substantially complete abbreviated new drug applications were previously submitted containing a certification that the same patent was invalid, unenforceable, or would not be infringed, approval of the subsequent abbreviated new drug application will be made effective no sooner than 180 days from whichever of the following dates is earlier:~~

~~(i) The date the applicant submitting the first application first commences commercial marketing of its drug product; or~~

~~(ii) The date of a decision of the court holding the relevant patent invalid, unenforceable, or not infringed.~~

(2) A first applicant must submit correspondence to its ANDA notifying FDA within 30 days of the date of its first commercial marketing of its drug product or the reference listed drug. If an applicant does not notify FDA, as required in this paragraph (c)(2), of this date, the date of first commercial marketing will be deemed to be the date of the drug product's approval. ~~(2) For purposes of paragraph (c)(1) of this section, the "applicant submitting the first application" is the applicant that submits an application that is both substantially complete and contains a certification that the patent was invalid, unenforceable, or not infringed prior to the submission of any other application for the same listed drug that is both substantially complete and contains the same certification. A "substantially complete" application must contain the results of any required bioequivalence studies, or, if applicable, a request for a waiver of such studies.~~

(3) ~~For purposes of paragraph (c)(1) of this section, if~~If FDA concludes that ~~the applicant submitting the first application application~~ a first applicant is not actively pursuing approval of its ~~abbreviated application~~ANDA, FDA ~~will make the approval of subsequent abbreviated applications~~may immediately approve an ANDA(s) of a subsequent applicant(s) if the ANDA(s) is~~effective if they are~~ otherwise eligible for ~~an immediately effective~~ approval.

~~(4) For purposes of paragraph (c)(1)(i) of this section, the applicant submitting the first application shall notify FDA of the date that it commences commercial marketing of its drug product. Commercial marketing commences with the first date of introduction or delivery for introduction into interstate commerce outside the control of the manufacturer of a drug product, except for investigational use under part 312 of this chapter, but does not include transfer of the drug product for reasons other than sale within the control of the manufacturer or application holder. If an applicant does not promptly notify FDA of such date, the effective date of approval shall be deemed to be the date of the commencement of first commercial marketing.~~

(d) *Delay due to exclusivity.* The ~~agency~~ Agency will also delay ~~the effective date of~~ the approval a 505(b)(2) application or ANDA if delay is required by the exclusivity provisions in § 314.108; section 527 of the Federal Food, Drug, and Cosmetic Act and § 316.31 of this chapter; section 505A of the Federal Food, Drug, and Cosmetic Act; or section 505E of the Federal Food, Drug, and Cosmetic Act. ~~of an abbreviated new drug application under section 505(j) of the act or a 505(b)(2) application if delay is required by the exclusivity provisions in § 314.108.~~ When the ~~effective date of an application~~approval of a 505(b)(2) application or ANDA is delayed under both this section and § 314.108;~~,~~ section 527 of the Federal Food, Drug, and Cosmetic Act and § 316.31 of this chapter; section 505A of the Federal Food, Drug, and Cosmetic Act; or section 505E of the Federal Food, Drug, and Cosmetic Act, the 505(b)(2) application or ANDA will be approved on latest of the days ~~the effective date will be the later of the 2 days~~ specified under this section and § 314.108~~.~~; section 527 of the Federal Food, Drug, and Cosmetic Act and § 316.31 of this chapter; section 505A of the Federal Food, Drug, and Cosmetic Act; or section 505E of the Federal Food, Drug, and Cosmetic Act, as applicable.

(e) *Notification of court actions or written consent to approval.* (1) The applicant ~~shall~~ must submit ~~a copy of the entry of the order or judgment to the Office of Generic Drugs (HFD-600), or to the appropriate division in the Office of New Drugs within 10 working days of a final judgment.~~the following information to FDA as applicable:

(i) A copy of any judgment by the court (district court or mandate of the court of appeals) or settlement order or consent decree signed and entered by the court (district court or court of appeals) finding a

patent described in paragraph (b)(3) of this section invalid, unenforceable, or not infringed, or finding the patent valid and infringed;

(ii) Written notification of whether or not any action by the court described in paragraph (e)(1)(i) of this section has been appealed within the time permitted for an appeal;

(iii) A copy of any order entered by the court terminating the 30-month or 7½-year period as described in paragraph (b)(3)(i), (ii), (vii), or (viii) of this section;

(iv) A copy of any written consent to approval by the patent owner or exclusive patent licensee described in paragraph (b)(3)(vi) of this section;

(v) A copy of any preliminary injunction described in paragraph (b)(3)(v) of this section, and a copy of any subsequent court order lifting the injunction; and

(vi) A copy of any court order pursuant to 35 U.S.C. 271(e)(4)(A) ordering that a 505(b)(2) application or ANDA may be approved no earlier than the date specified (irrespective of whether the injunction relates to a patent described in paragraph (b)(3) of this section).

(2) All information required by paragraph (e)(1) of this section must be sent to the applicant's NDA or ANDA, as appropriate, within 14 days of the date of entry by the court, the date of appeal or expiration of the time for appeal, or the date of written consent to approval, as applicable.

(f) ~~*Computation of 45-day time clock.*~~*Forty-five day period after receipt of notice of paragraph IV certification -* (1) *Computation of 45-day time clock.* The 45-day clock described in paragraph (b)(3) of this section as to each recipient require to receive notice of paragraph IV certification under § 314.52 or § 314.95 begins on the day after the date of receipt of the applicant's notice of paragraph IV certification by the ~~patent owner or its representative, and by the approved application holder.~~recipient. When the 45th day falls on Saturday, Sunday, or a Federal holiday, the 45th day will be the next day that is not a Saturday, Sunday, or a Federal holiday.

(2) *Notification of filing of legal action.* The ~~abbreviated new drug applicant or the~~ 505(b)(2) or ANDA applicant ~~shall~~ must notify ~~FDA~~FDA in writing within 14 days ~~immediately~~ of the filing of any legal action filed within 45 days of receipt of the notice of paragraph IV certification by any recipient. A 505(b)(2) applicant must send the notification to its NDA. An ANDA applicant must send the notification to its ANDA. The notification to FDA of the legal action must include:

~~If the applicant submitting the abbreviated new drug application or the 505(b)(2) application or patent owner or its representative does not notify FDA in writing before the expiration of the 45-day time period or the completion of the~~

~~agency's review of the application, whichever occurs later, that a legal action for patent infringement was filed within 45 days of receipt of the notice of certification, approval of the abbreviated new drug application or the 505(b)(2) application will be made effective immediately upon expiration of the 45 days or upon completion of the agency's review and approval of the application, whichever is later. The notification to FDA of the legal action shall include:~~

(A~~i~~) The ~~abbreviated new drug application or~~ 505(b)(2) application or ANDA number.

(~~ii~~B) The name of the ~~abbreviated new drug or~~ 505(b)(2) ~~application~~ or ANDA applicant.

(~~iii~~C) The established name of the drug product or, if no established name exists, the name(s) of the active ingredient(s), the drug product's strength, and dosage form.

(~~iv~~D) A ~~certification~~ statement that an action for patent infringement identified by court, case number, and the patent number(s) of the patent(s) at issue in the action, has been filed in an appropriate court on a specified date.

(ii) A patent owner or NDA holder (or its representative(s)) may also notify FDA of the filing of any legal action for patent infringement. The notice should contain the information and be sent to the offices or divisions described in paragraph (f)(2)(i) of this section.

(iii) If the 505(b)(2) or ANDA applicant, the patent owner(s), the NDA holder, or its representative(s) does not notify FDA in writing before the expiration of the 45-day time period or the completion of the Agency's review of the 505(b)(2) application or ANDA, whichever occurs later, that a legal action for patent infringement was filed within 45 days of receipt of the notice of paragraph IV certification, the 505(b)(2) application or ANDA may be approved upon expiration of the 45-day period (if the 505(b)(2) or ANDA applicant confirms that a legal action for patent infringement has not been filed) or upon completion of the Agency's review of the 505(b)(2) application or ANDA, whichever is later ~~The applicant of an abbreviated new drug application shall send the notification to FDA's Office of Generic Drugs (HFD-600). A 505(b)(2) applicant shall send the notification to the appropriate division in the Office of New Drugs reviewing the application. A patent owner or its representative may also notify FDA of the filing of any legal action for patent infringement. The notice should contain the information and be sent to the offices or divisions described in this paragraph.~~

(3) *Waiver.* If the patent owner or ~~approved application~~NDA holder who is an exclusive patent licensee (or its representative(s)) waives its opportunity to file a legal action for patent infringement within 45 days of a receipt of the notice of certification and the patent owner or ~~approved application~~NDA holder who is an exclusive patent licensee (or its

representative(s)) submits to FDA a valid waiver before the 45 days elapse, ~~approval of the abbreviated new drug application or~~ the 505(b)(2) application or ANDA may be approved upon ~~will be made effective~~ upon completion of the ~~agency's~~ Agency's review and approval of the ~~application~~NDA or ANDA. FDA will only accept a waiver in the following form:

(*NAME OF PATENT OWNER or NDA HOLDER WHO IS AN~~OR~~ EXCLUSIVE PATENT LICENSEE OR ITS REPRESENTATIVE(S)*) HAS RECEIVED NOTICE FROM (*NAME OF APPLICANT*) UNDER (*SECTION 505(B)(3) OR 505(J)(2)(B) OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT*) AND DOES NOT INTEND TO FILE AN ACTION FOR PATENT INFRINGEMENT AGAINST (*NAME OF APPLICANT*) CONCERNING THE DRUG (*NAME OF DRUG*) BEFORE (*DATE ON WHICH 45 DAYS ELAPSES*). (*NAME OF PATENT OWNER OR NDA HOLDER WHO IS AN EXCLUSIVE PATENT LICENSEE*) WAIVES THE OPPORTUNITY PROVIDED BY (*SECTION 505(C)(3)(C) OR 505(J)(5)(B)(III) OF THE ~~ACT~~FEDERAL FOOD, DRUG, AND COSMETIC ACT*) AND DOES NOT OBJECT TO FDA'S APPROVAL OF (*NAME OF APPLICANT*)'S (*505(B)(2) APPLICATION OR ~~ABBREVIATED NEW DRUG APPLICATION~~ANDA*) FOR (*NAME OF DRUG*) WITH AN ~~IMMEDIATE EFFECTIVE~~APPROVAL DATE ON OR AFTER THE DATE OF THIS ~~LETTER~~SUBMISSION.

(g) Conversion of approval to tentative approval. If FDA issues an approval letter in error or a court enters an order requiring, in the case of an already approved 505(b)(2) application or ANDA, that the date of approval be delayed, FDA will convert the approval to a tentative approval if appropriate.

21 C.F.R. § 314.108 – NEW DRUG PRODUCT EXCLUSIVITY

(a) *Definitions.* The definitions in § 314.3 and the following definitions of terms apply to this section:

Active moiety means 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.

Approved under section 505(b) means an ~~application~~ NDA submitted under section 505(b) and approved on or after October 10, 1962, or an application that was "deemed approved" under section 107(c)(2) of Pub. L. 87-781.

Bioavailability study means a study to determine the bioavailability or the pharmacokinetics of a drug.

Clinical investigation means any experiment other than a bioavailability study in which a drug is administered or dispensed to, or used on, human subjects.

Conducted or sponsored by the applicant with regard to an investigation means that before or during the investigation, the applicant was named in Form FDA-1571 filed with FDA as the sponsor of the investigational new drug application under which the investigation was conducted, or the applicant or the applicant's predecessor in interest, provided substantial support for the investigation. To demonstrate "substantial support," an applicant must either provide a certified statement from a certified public accountant that the applicant provided 50 percent or more of the cost of conducting the study or provide an explanation why FDA should consider the applicant to have conducted or sponsored the study if the applicant's financial contribution to the study is less than 50 percent or the applicant did not sponsor the investigational new drug. A predecessor in interest is an entity, e.g., a corporation, that the applicant has taken over, merged with, or purchased, or from which the applicant has purchased all rights to the drug. Purchase of nonexclusive rights to a clinical investigation after it is completed is not sufficient to satisfy this definition.

Date of approval means the date on the letter from FDA stating that the new drug application is approved, whether or not final printed labeling or other materials must yet be submitted as long as approval of such labeling or materials is not expressly required. "Date of approval" refers only to a final approval and not to a tentative approval that may become effective at a later date.

Essential to approval means, with regard to an investigation, that there are no other data available that could support approval of the ~~application~~NDA.

FDA means the Food and Drug Administration.

New chemical entity means a drug that contains no active moiety that has been approved by FDA in any other ~~application~~ NDA submitted under section 505(b) of the ~~act~~Federal Food, Drug, and Cosmetic Act.

New clinical investigation means an investigation in humans the results of which have not been relied on by FDA to demonstrate substantial evidence of effectiveness of a previously approved drug product for any indication or of safety for a new patient population and do not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness or safety in a new patient population of a previously approved drug product. For purposes of this section, data from a clinical investigation previously submitted for use in the comprehensive evaluation of the safety of a drug product

but not to support the effectiveness of the drug product would be considered new.

(b) *Submission of and ~~effective date~~timing of ~~approval of an abbreviated new drug application submitted under section 505(j) of the act or~~ a 505(b)(2) application or ANDA.* (1) [Reserved]

(2) If a drug product that contains a new chemical entity was approved after September 24, 1984, in an ~~application~~ NDA submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act~~act~~, no person may submit a 505(b)(2) application or ~~abbreviated new drug application~~ANDA under section 505(j) of the Federal Food, Drug, and Cosmetic Act ~~act~~ for a drug product that contains the same active moiety as in the new chemical entity for a period of 5 years from the date of approval of the first approved ~~new drug application~~NDA, except that the 505(b)(2) application or ~~abbreviated application~~ANDA may be submitted after 4 years if it contains a certification of patent invalidity or noninfringement described in § 314.50(i)(1)(i)(A)(*4*) or § 314.94(a)(12)(i)(A)(*4*).

(3) The approval of a 505(b)(2) application or ~~abbreviated application~~ANDA described in paragraph (b)(2) of this section will ~~become effective~~occur as provided in § 314.107(b)(1) or ~~(b)~~(2), unless the owner of a patent that claims the drug, the patent owner's representative, or exclusive licensee brings suit for patent infringement against the applicant during the 1-year period beginning 48 months after the date of approval of the ~~new drug application~~NDA for the new chemical entity and within 45 days after receipt of the notice described at § 314.52 or § 314.95, in which case, approval of the 505(b)(2) application or ~~abbreviated application~~ANDA will ~~be made effective~~occur as provided in § 314.107(b)(3).

(4) If an ~~application~~NDA:

(i) Was submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act~~act~~;

(ii) Was approved after September 24, 1984;

(iii) Was for a drug product that contains an active moiety that has been previously approved in another ~~application~~ NDA under section 505(b) of the Federal Food, Drug, and Cosmetic Act~~act~~; and

(iv) Contained reports of new clinical investigations (other than bioavailability studies) conducted or sponsored by the applicant that were essential to approval of the application, ~~the agency will not make effective~~ for a period of 3 years after the date of approval of the application, the Agency will not approve ~~the approval of~~ a 505(b)(2) application or an ~~abbreviated new drug application~~ANDA for the conditions of approval of the ~~original application~~NDA, or an ~~abbreviated new drug application~~ANDA submitted pursuant to an approved petition under section 505(j)(2)(C) of the Federal Food, Drug, and Cosmetic Act ~~act~~ that relies

on the information supporting the conditions of approval of an original ~~new drug application~~NDA.

(5) If a supplemental ~~application~~NDA:

(i) Was approved after September 24, 1984; and

(ii) Contained reports of new clinical investigations (other than bioavailability studies) that were conducted or sponsored by the applicant that were essential to approval of the supplemental ~~application~~NDA, ~~the agency will not make effective~~ for a period of 3 years after the date of approval of the supplemental application, the Agency will not approve ~~the approval of~~ a 505(b)(2) application or an ~~abbreviated new drug application~~ANDA for a change, or an ~~abbreviated new drug application~~ANDA submitted pursuant to an approved petition under section 505(j)(2)(C) of the Federal Food, Drug, and Cosmetic Act ~~act~~ that relies on the information supporting a change approved in the supplemental ~~new drug application~~NDA.

21 C.F.R. § 314.125 – REFUSAL TO APPROVE AN ~~APPLICATION~~NDA

(a) The Food and Drug Administration will refuse to approve the application and for a new drug give the applicant written notice of an opportunity for a hearing under § 314.200 on the question of whether there are grounds for denying approval of the application under section 505(d) of the act, if:

(1) FDA sends the applicant a complete response letter under § 314.110;

(2) The applicant requests an opportunity for hearing for a new drug on the question of whether the application is approvable; and

(3) FDA finds that any of the reasons given in paragraph (b) of this section apply.

(b) FDA may refuse to approve an ~~application~~ NDA for any of the following reasons, unless the requirement has been waived under § 314.90:

(1) The methods to be used in, and the facilities and controls used for, the manufacture, processing, packing, or holding of the drug substance or the drug product are inadequate to preserve its identity, strength, quality, purity, stability, and bioavailability.

(2) The investigations required under section 505(b) of the act do not include adequate tests by all methods reasonably applicable to show whether or not the drug is safe for use under the conditions prescribed, recommended, or suggested in its proposed labeling.

(3) The results of the tests show that the drug is unsafe for use under the conditions prescribed, recommended, or suggested in its proposed labeling or the results do not show that the drug product is safe for use under those conditions.

(4) There is insufficient information about the drug to determine whether the product is safe for use under the conditions prescribed, recommended, or suggested in its proposed labeling.

(5) There is a lack of substantial evidence consisting of adequate and well-controlled investigations, as defined in § 314.126, that the drug product will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in its proposed labeling.

(6) The proposed labeling is false or misleading in any particular.

(7) The application contains an untrue statement of a material fact.

(8) The drug product's proposed labeling does not comply with the requirements for labels and labeling in part 201.

(9) The application does not contain bioavailability or bioequivalence data required under part 320 of this chapter.

(10) A reason given in a letter refusing to file the application under § 314.101(d), if the deficiency is not corrected.

(11) The drug will be manufactured or processed in whole or in part in an establishment that is not registered and not exempt from registration under section 510 of the act and part 207.

(12) The applicant does not permit a properly authorized officer or employee of the Department of Health and Human Services an adequate opportunity to inspect the facilities, controls, and any records relevant to the application.

(13) The methods to be used in, and the facilities and controls used for, the manufacture, processing, packing, or holding of the drug substance or the drug product do not comply with the current good manufacturing practice regulations in parts 210 and 211.

(14) The application does not contain an explanation of the omission of a report of any investigation of the drug product sponsored by the applicant, or an explanation of the omission of other information about the drug pertinent to an evaluation of the application that is received or otherwise obtained by the applicant from any source.

(15) A nonclinical laboratory study that is described in the application and that is essential to show that the drug is safe for use under the conditions prescribed, recommended, or suggested in its proposed labeling was not conducted in compliance with the good laboratory practice regulations in part 58 of this chapter and no reason for

the noncompliance is provided or, if it is, the differences between the practices used in conducting the study and the good laboratory practice regulations do not support the validity of the study.

(16) Any clinical investigation involving human subjects described in the application, subject to the institutional review board regulations in part 56 of this chapter or informed consent regulations in part 50 of this chapter, was not conducted in compliance with those regulations such that the rights or safety of human subjects were not adequately protected.

(17) The applicant or contract research organization that conducted a bioavailability or bioequivalence study described in § 320.38 or § 320.63 of this chapter that is contained in the application refuses to permit an inspection of facilities or records relevant to the study by a properly authorized officer or employee of the Department of Health and Human Services or refuses to submit reserve samples of the drug products used in the study when requested by FDA.

(18) For a new drug, the application failed to contain the patent information required by section 505(b)(1) of the act.

(19) The 505(b)(2) application failed to contain a patent certification or statement with respect to each listed patent for a drug product approved in an NDA that: (i) Is pharmaceutically equivalent to the drug product for which the original 505(b)(2) application is submitted; and (ii) Was approved before the original 505(b)(2) application was submitted.

(c) For drugs intended to treat life-threatening or severely-debilitating illnesses that are developed in accordance with §§ 312.80 through 312.88 of this chapter, the criteria contained in paragraphs (b) (3), (4), and (5) of this section shall be applied according to the considerations contained in § 312.84 of this chapter.

21 C.F.R. § 314.127 – REFUSAL TO APPROVE AN ~~ABBREVIATED NEW DRUG APPLICATION~~ANDA

(a) FDA will refuse to approve an ~~abbreviated application~~ANDA for a new drug under section 505(j) of the ~~act~~ Federal Food, Drug, and Cosmetic Act for any of the following reasons, unless the requirement has been waived under § 314.99:

(1) The methods used in, or the facilities and controls used for, the manufacture, processing, and packing of the drug product are inadequate to ensure and preserve its identity, strength, quality, and purity.

(2) Information submitted with the ~~abbreviated new drug application~~ANDA is

insufficient to show that each of the proposed conditions of use has been previously approved for the listed drug referred to in the ~~application~~ANDA.

(3)(i) If the reference listed drug has only one active ingredient, information submitted with the abbreviated new drug application is insufficient to show that the active ingredient is the same as that of the reference listed drug;

(ii) If the reference listed drug has more than one active ingredient, information submitted with the abbreviated new drug application is insufficient to show that the active ingredients are the same as the active ingredients of the reference listed drug; or

(iii) If the reference listed drug has more than one active ingredient and if the abbreviated new drug application is for a drug product that has an active ingredient different from the reference listed drug:

(A) Information submitted with the abbreviated new drug application is insufficient to show:

(*1*) That the other active ingredients are the same as the active ingredients of the reference listed drug; or

(*2*) That the different active ingredient is an active ingredient of a listed drug or a drug that does not meet the requirements of section 201(p) of the act; or

(B) No petition to submit an abbreviated application for the drug product with the different active ingredient was approved under § 314.93.

(4)(i) If the abbreviated new drug application is for a drug product whose route of administration, dosage form, or strength purports to be the same as that of the listed drug referred to in the abbreviated new drug application, information submitted in the abbreviated new drug application is insufficient to show that the route of administration, dosage form, or strength is the same as that of the reference listed drug; or

(ii) If the abbreviated new drug application is for a drug product whose route of administration, dosage form, or strength is different from that of the listed drug referred to in the application, no petition to submit an abbreviated new drug application for the drug product with the different route of administration, dosage form, or strength was approved under § 314.93.

(5) If the abbreviated new drug application was submitted under the approval of a petition under § 314.93, the abbreviated new drug application did not contain the information required by FDA with respect to the active ingredient, route of administration, dosage form, or strength that is not the same as that of the reference listed drug.

(6)(i) Information submitted in the abbreviated new drug application is insufficient to show that the drug product is bioequivalent to the listed drug referred to in the abbreviated new drug application; or

(ii) If the abbreviated new drug application was submitted under a petition approved under § 314.93, information submitted in the abbreviated new drug application is insufficient to show that the active ingredients of the drug product are of the same pharmacological or therapeutic class as those of the reference listed drug and that the drug product can be expected to have the same therapeutic effect as the reference listed drug when administered to patients for each condition of use approved for the reference listed drug.

(7) Information submitted in the abbreviated new drug application is insufficient to show that the labeling proposed for the drug is the same as the labeling approved for the listed drug referred to in the abbreviated new drug application except for changes required because of differences approved in a petition under § 314.93 or because the drug product and the reference listed drug are produced or distributed by different manufacturers or because aspects of the listed drug's labeling are protected by patent, or by exclusivity, and such differences do not render the proposed drug product less safe or effective than the listed drug for all remaining, nonprotected conditions of use.

(8)(i) Information submitted in the ~~abbreviated new drug application~~ANDA ~~of~~ or any other information available to FDA shows that:

(A) The inactive ingredients of the drug product are unsafe for use, as described in paragraph (a)(8)(ii) of this section, under the conditions prescribed, recommended, or suggested in the labeling proposed for the drug product; or

(B) The composition of the drug product is unsafe, as described in paragraph (a)(8)(ii) of this section, under the conditions prescribed, recommended, or suggested in the proposed labeling because of the type or quantity of inactive ingredients included or the manner in which the inactive ingredients are included.

(ii)(A) FDA will consider the inactive ingredients or composition of a drug product unsafe and refuse to approve an abbreviated new drug application under paragraph (a)(8)(i) of this section if, on the basis of information available to the agency, there is a reasonable basis to conclude that one or more of the inactive ingredients of the proposed drug or its composition raises serious questions of safety or efficacy. From its experience with reviewing inactive ingredients, and from other information available to it, FDA may identify changes in inactive ingredients or composition that may adversely affect a drug product's safety or efficacy. The inactive ingredients or composition of a proposed drug product will be considered to raise serious questions of safety or efficacy if the product incorporates one or more of these changes. Examples of the changes that may raise serious questions of safety or efficacy include, but are not limited to, the following:

(*1*) A change in an inactive ingredient so that the product does not comply with an official compendium.

(*2*) A change in composition to include an inactive ingredient that has not been previously approved in a drug product for human use by the same route of administration.

(*3*) A change in the composition of a parenteral drug product to include an inactive ingredient that has not been previously approved in a parenteral drug product.

(*4*) A change in composition of a drug product for ophthalmic use to include an inactive ingredient that has not been previously approved in a drug for ophthalmic use.

(*5*) The use of a delivery or a modified release mechanism never before approved for the drug.

(*6*) A change in composition to include a significantly greater content of one or more inactive ingredients than previously used in the drug product.

(*7*) If the drug product is intended for topical administration, a change in the properties of the vehicle or base that might increase absorption of certain potentially toxic active ingredients thereby affecting the safety of the drug product, or a change in the lipophilic properties of a vehicle or base, e.g., a change from an oleaginous to a water soluble vehicle or base.

(B) FDA will consider an inactive ingredient in, or the composition of, a drug product intended for parenteral use to be unsafe and will refuse to approve the ~~abbreviated new drug application~~ANDA unless it contains the same inactive ingredients, other than preservatives, buffers, and antioxidants, in the same concentration as the listed drug, and, if it differs from the listed drug in a preservative, buffer, or antioxidant, the ~~application~~ ANDA contains sufficient information to demonstrate that the difference does not affect the safety or efficacy of the drug product.

(C) FDA will consider an inactive ingredient in, or the composition of, a drug product intended for ophthalmic or otic use unsafe and will refuse to approve the ~~abbreviated new drug application~~ANDA unless it contains the same inactive ingredients, other than preservatives, buffers, substances to adjust tonicity, or thickening agents, in the same concentration as the listed drug, and if it differs from the listed drug in a preservative, buffer, substance to adjust tonicity, or thickening agent, the ~~application~~ ANDA contains sufficient information to demonstrate that the difference does not affect the safety or efficacy of the drug product and the labeling does not claim any therapeutic advantage over or difference from the listed drug.

(9) Approval of the listed drug referred to in the abbreviated new drug application has been withdrawn or suspended for grounds described in § 314.150(a) or FDA

has published a notice of opportunity for hearing to withdraw approval of the reference listed drug under § 314.150(a).

(10) Approval of the listed drug referred to in the abbreviated new drug application has been withdrawn under § 314.151 or FDA has proposed to withdraw approval of the reference listed drug under § 314.151(a).

(11) FDA has determined that the reference listed drug has been withdrawn from sale for safety or effectiveness reasons under § 314.161, or the reference listed drug has been voluntarily withdrawn from sale and the agency has not determined whether the withdrawal is for safety or effectiveness reasons, or approval of the reference listed drug has been suspended under § 314.153, or the agency has issued an initial decision proposing to suspend the reference listed drug under § 314.153(a)(1).

(12) The abbreviated new drug application does not meet any other requirement under section 505(j)(2)(A) of the act.

(13) The abbreviated new drug application contains an untrue statement of material fact.

(b) FDA may refuse to approve an abbreviated application for a new drug if the applicant or contract research organization that conducted a bioavailability or bioequivalence study described in § 320.63 of this chapter that is contained in the abbreviated new drug application refuses to permit an inspection of facilities or records relevant to the study by a properly authorized officer of employee of the Department of Health and Human Services or refuses to submit reserve samples of the drug products used in the study when requested by FDA.

(14) For an ANDA submitted pursuant to an approved petition under § 10.30 of this chapter and § 314.93, an NDA subsequently has been approved for the change described in the approved petition.

21 C.F.R. § 320.1 – DEFINITIONS

The definitions contained in § 314.3 of this chapter apply to those terms when used in this part.

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

~~(b) *Drug product* means a finished dosage form, e.g., tablet, capsule, or solution, that contains the active drug~~

ingredient, generally, but not necessarily, in association with inactive ingredients.

(c) *Pharmaceutical equivalents* means drug products in identical dosage forms that contain identical amounts of the identical active drug ingredient, *i.e.*, the same salt or ester of the same therapeutic moiety, 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.

(d) *Pharmaceutical alternatives* means 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.

(e) *Bioequivalence* means 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 alternatives 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.

(f) *Bioequivalence requirement* means a requirement imposed by the Food and Drug Administration for in vitro and/or in vivo testing of specified drug products which must be satisfied as a condition of marketing.

(g) *Same drug product formulation* means 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.The definitions contained in § 314.3 of this chapter apply to those terms when used in this part.

21 C.F.R. § 320.23 – BASIS FOR MEASURING IN VIVO BIOAVAILABILITY OR DEMONSTRATING BIOEQUIVALENCE

(a)(1) The in vivo bioavailability of a drug product is measured if the product's rate and extent of absorption, as determined by comparison of measured parameters, e.g., concentration of the active drug ingredient in the blood, urinary excretion rates, or pharmacological effects, do not indicate a significant difference from the reference material's rate and extent of absorption. 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 action.

(2) Statistical techniques used must~~shall~~ be of sufficient sensitivity to detect differences in rate and extent of absorption that are not attributable to subject variability.

(3) A drug product that differs from the reference material in its rate of absorption, but not in its extent of absorption, may be considered to be bioavailable if the difference in the rate of absorption is intentional, is appropriately reflected in the labeling, is not essential to the attainment of effective body drug concentrations on chronic use, and is considered medically insignificant for the drug product.

(b)(1) Two drug products will be considered bioequivalent drug products if they are pharmaceutical equivalents or pharmaceutical alternatives whose rate and extent of absorption do not show a significant difference when administered at the same molar dose of the active moiety under similar experimental conditions, either single dose or multiple dose. Some pharmaceutical equivalents or pharmaceutical alternatives may be equivalent in the extent of their absorption but not in their rate of absorption and yet may be considered bioequivalent because such differences in the rate of absorption are intentional and are reflected in the labeling, are not essential to the attainment of effective body drug concentrations on chronic use, and are considered medically insignificant for the particular drug product studied.

(2) For drug products that are not intended to be absorbed into the bloodstream, bioequivalence may be demonstrated by scientifically valid methods that are expected to detect a significant difference between the drug and the listed drug in safety and therapeutic effect.