(2) If FDA authorizes shipment of the drug for use in clinical investigation. Authorization may be obtained as follows:

(i) Through submission to the International Affairs Staff (HFY-50), Associate Commissioner for Health Affairs, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, of a written request from the person that seeks to export the drug. A request must provide adequate information about the drug to satisfy FDA that the drug is appropriate for the proposed investigational use in humans, that the drug will be used for investigational purposes only, and that the drug may be legally used by that consignee in the importing country for the proposed investigational use. The request shall specify the quantity of the drug to be shipped per shipment and the frequency of expected shipments. If FDA authorizes exportation under this paragraph, the agency shall concurrently notify the government of the importing country of such authorization; or

(ii) Through submission to the International Affairs Staff (HFY-50), Associate Commissioner for Health Affairs, FDA, of a formal request from an authorized official of the government of the country to which the drug is proposed to be shipped. Such a request must specify that the foreign government has adequate information about the drug and the proposed investigational use, that the drug will be used for investigational purposes only, and that the foreign government is satisfied that the drug may legally be used by the intended consignee in that country. Such a request shall specify the quantity of drug to be shipped per shipment and the frequency of expected shipments.

(iii) Authorization to export an investigational drug under paragraph (b)(2) (i) or (ii) of this section may be revoked by FDA if the agency finds that the conditions underlying its authorization are no longer met.

(3) This paragraph applies only where the drug is to be used for the purpose of clinical investigation. Export of an investigational drug for commercial marketing or for use in routine medical practice is not permitted.

(Approved by the Office of Management and Budget under control number 0910—0162)

(Secs. 501, 502, 503, 505, 506, 507, 701, 52 Stat. 1049-1053 as amended, 1055-1056 as amended, 55 Stat. 851, 59 Stat. 463 as amended (21 U.S.C. 351, 352, 353, 356, 357, 371); secs. 351, 58 Stat. 702 as amended (42 U.S.C. 262).

[49 FR 2097, Jan. 18, 1984]

PART 314—APPLICATIONS FOR FDA APPROVAL TO MARKET A NEW DRUG OR AN ANTIBIOTIC DRUG

Subpart A—General Provisions

Subpart B—Applications

Subpart C—FDA Action on Applications

AUTHORITY: Secs. 501, 502, 503, 505, 506, 507, 701, 52 Stat. 1049-1053 as amended, 1055-1056 as amended, 55 Stat. 851, 59 Stat. 463 as amended (21 U.S.C. 351, 352, 353, 355, 356, 357, 371); 21 CFR 5.10, 5.11.

SOURCE: 50 FR 7493, Feb. 22, 1985, unless otherwise noted.

Subpart A—General Provisions

§ 314.1 Scope of this part.

(a) This part sets forth procedures and requirements for the submission to, and the review by, the Food and Drug Administration of applications and abbreviated applications, as well as amendments, supplements, and postmarketing reports to them, by persons seeking or holding approval from FDA of the following:

(1) An application under section 505 of the Federal Food, Drug, and Cosmetic Act to market a new drug.

(2) An application under section 507 of the Federal Food, Drug, and Cosmetic Act to market an antibiotic drug.

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

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

§ 314.2 Purpose.

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

§ 314.3 Definitions.

(a) The definitions and interpretations contained in section 201 of the act apply to those terms when used in this part.

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

"Act" means the Federal Food, Drug, and Cosmetic Act (sections 201-901, 52 Stat. 1040 et seq., as amended (21 U.S.C. 301-392)).

"Applicant" means any person who submits an application or abbreviated application or an amendment or supplement to them under this part to obtain Food and Drug Administration approval of a new drug or an antibiotic drug and any person who owns an approved application.

"Application" means both the application described under § 314.50 and the abbreviated application under § 314.55, including all amendments and supplements.

"Approvable letter" means a written communication to an applicant from FDA stating that the agency will approve the application if specific additional information or material is submitted or specific conditions are met. An approvable letter does not constitute approval of any part of an application and does not permit marketing

of the drug that is the subject of the application.

"Approval letter" means a written communication to an applicant from FDA approving an application. An approval letter permits marketing of the drug product that is the subject of the application.

"Drug product" means a finished dosage form, for example, tablet, capsule, or solution, that contains a drug substance, generally, but not necessarily, in association with one or more other ingredients.

"Drug substance" means 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 of any function of the human body, but does not include intermediates used in the synthesis of such ingredient.

"FDA" means the Food and Drug Administration.

"Not approvable letter" means a written communication to an applicant from FDA stating that the agency does not consider the application approvable because one or more deficiencies in the application preclude the agency from approving it.

Subpart B—Applications

§ 314.50 Content and format of an application.

Applications, including abbreviated applications, and supplements to approved applications are required to be submitted in the form and contain the information, as appropriate for the particular submission, required under this section. Two copies of the application are required, an archival copy and a review copy. An application 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. Other applications 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 for a duplicate of a marketed drug product (such as a "paper NDA," which relies primarily on published literature to provide substantial evidence of effectiveness and adequate scientific evidence of safety for the claimed indications), an abbreviated application, an amendment, and a supplement. The application 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. The Food and Drug Administration will maintain guidelines on the format and content of applications to assist applicants in their preparation.

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

(1) The name and address of the applicant; the date of the application; the application number if previously issued (for example, if the application 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 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; and the drug product's proposed indications for use.

(2) A statement whether the submission is an original submission, a resubmission, an abbreviated application under § 314.55, 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 sign the application. If the person signing the application does not reside or have a place of business within the United States, the application is required to contain the name and address of, and be counter-

signed 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 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 is required to contain a summary of the application in enough detail that the reader may gain a good general understanding of the data and information in the application, including an understanding of the quantitative aspects of the data. The summary is not required for abbreviated applications under § 314.55 and supplements under § 314.70. Resubmissions of an application should contain an updated summary, as appropriate. The summary should discuss all aspects of the application, 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, FDA may furnish the summary to FDA advisory committee members and agency officials whose duties require an understanding of the application. 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 is approved.

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

(i) The proposed text of the labeling for the drug, with annotations to the information in the summary and technical sections of the application that support the inclusion of each statement in the labeling, and, if the application is for a prescription drug, statements describing the reasons for omitting a section or subsection of the labeling format in § 201.57.

(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.

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

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

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

(viii) A summary of the clinical data section of the application, 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 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 or whether grounds exist under section 505(d) or 507 of the act to refuse to ap-

prove the application. 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 such specifications and analytical methods as are necessary to assure the identity, strength, quality, and purity of the drug substance and the bioavailability of the drug products made from the substance, including, for example, specifications relating to stability, sterility, particle size, and crystalline form. The application may provide additionally for the use of alternatives to meet any of these requirements, including alternative sources, process controls, methods, and specifications. Reference to the current edition of the U.S. Pharmacopeia and the National Formulary may satisfy relevant requirements in this paragraph.

(ii) *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; a statement of the specifications and analytical methods for each component; the name and address of each manufacturer the drug product; 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, for example, specifications relating to sterility, dissolution rate, containers and closure systems; and stability data with proposed expiration dating. The application may provide additionally for the use of alternatives to meet any of these requirements, including alternative components, manufacturing and packaging procedures, in-process controls, methods, and specifications. Reference to the current edition of the U.S. Pharmacopeia and the National Formulary may satisfy relevant requirements in this paragraph.

(iii) *Environmental impact.* The application is required to contain either a claim for categorical exclusion under § 25.24 of this chapter or an environmental assessment under § 25.31 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. FDA will review such early submissions as resources permit.

(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 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 describes in the chemistry, manufacturing, and controls section specifications or analytical methods 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 specification or analytical methods, 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 methods (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, 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, and modifications for specific subgroups (for example, pediatrics, geriatrics, patients with renal failure).

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

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

verse effects of the drug, clinically significant drug/drug interactions, and other safety considerations, such as data from epidemiological studies of related drugs. A description of any statistical analyses performed in analyzing safety data should also be included, unless already included under paragraph (a)(5)(ii) of this section.

(*b*) The applicant shall, under section 505(i) of the act, update periodically its pending application 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. These "safety update reports" are required to include the same kinds of information (from clinical studies, animal studies, and other sources) and are required to 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 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 submit these reports (*1*) 4 months after the initial submission; (*2*) following receipt of an approvable letter; and (*3*) at other times as requested by FDA. Prior to the submission of 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.

(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.

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

(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 to determine whether the drug substance and the drug product meet the specifications given in the application:

(*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 submit the following in the archival copy of the application:

(i) Three copies of the analytical methods 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 methods. 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 (4 copies of draft labeling or 12 copies of final printed labeling).

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

(1) *Case report tabulations.* The application 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 § 312.1(a)(2), Form FDA-1571), tabulations of the data from the earliest clinical pharmacology studies (Phase 1 studies as described in § 312.1(a)(2), Form FDA-1571), 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. 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, in accordance with paragraph (f)(3) of this section.

(2) *Case report forms.* The application 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 submit to FDA additional case report forms and tabulations needed to conduct a proper review of the application, as requested by the director of the FDA division responsible for reviewing the application. 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 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.

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

(h) *Format of an original application.* (1) The applicant shall submit a complete archival copy of the application 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 to permit individual reviewers to refer to information that is not contained in their particular technical sections of the application, to give other agency personnel access to the application for official business, and to maintain in one place a complete copy of the application. An applicant may submit on microfiche the portions of the archival copy of the application described in paragraphs (b) through (d) of this section. Information relating to samples and labeling, described in paragraph (e) of this section, is required to be submitted in hard copy. Tabulations of patient data and case report forms, described in paragraph (f) of this section, may be submitted on microfiche only if the applicant and FDA agree. If FDA agrees, the applicant may use another suitable microform system.

(2) The applicant shall submit a review copy of the application. Each of the technical sections (described in paragraphs (d) (1) through (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. The applicant may obtain from FDA sufficient folders to bind the archival and review copies of the application.

(Collection of information requirements approved by the Office of Management and Budget under number 0910-0001)

[50 FR 7493, Feb. 22, 1985; 50 FR 14212, Apr. 11, 1985, as amended at 50 FR 16668, Apr. 26, 1985; 50 FR 21238, May 23, 1985]

§ 314.55 Abbreviated application.

(a) An abbreviated application is an application in which reports of nonclinical laboratory studies and reports of clinical investigations (except those pertaining to in vivo bioavailability of the drug product) may be omitted. The information may be omitted when the Food and Drug Administration has determined that the information already available to it is adequate to establish that a particular dosage form of a drug meets the statutory standards for safety and effectiveness. An abbreviated application will usually be reserved for duplicates of drug products previously approved under a full application under § 314.50. An abbreviated application is not required to comply with the requirements in § 314.50 (c), (d)(2), (4), (5), (6), and (f).

(b) FDA will file an abbreviated application only if it has made a finding that an abbreviated application is suitable for a drug product. If FDA finds that a drug product may be approved for marketing on the basis of an abbreviated application, it will make that finding publicly available, as follows:

(1) If the finding applies to a broad category of drug products, the agency will amend § 314.56 to identify the category in that section.

(2) If the finding applies to a drug product because it is so closely related to a product for which an abbreviated application is suitable that the same conclusions about safety and effectiveness apply to it, the agency will make the finding public by updating its list of drug products for which abbreviated applications are suitable. The list is available from the National Technical Information Service, Department of Commerce, 5285 Port Royal Rd., Springfield, VA 22161.

(3) If the finding applies to duplicates of a drug product that is subject to FDA's Drug Efficacy Study Implementation program (a review of drug products approved as safe between 1938 and 1962), the agency will make that finding public through a notice published in the FEDERAL REGISTER.

(c)(1) A finding by FDA that an abbreviated application is suitable for a drug product applies only to a product that is the same in active ingredient,

dosage form and strength, route of administration, and conditions of use as the drug product that was the subject of the finding. For a drug product that is similar but different in one or more of these characteristics, an abbreviated application will be accepted only if FDA has made a separate finding of suitability. However, filing of an abbreviated application for a drug product does not signify that the product is safe and effective until the application is approved.

(2) A finding that a drug product is a new drug because it is similar to a product that is a new drug, and is therefore subject to the requirements of this part, does not include a finding that an abbreviated application is suitable for the similar product.

(3) A finding that a single-active-entity drug product is safe and effective and that an abbreviated application is suitable is not a basis for determining that a combination drug product containing that entity as one of its ingredients is either safe or effective or that an abbreviated application is suitable. The finding also is not a basis for determining that the combination drug product meets all of the requirements for combination drugs as described in § 300.50.

(d) (1) A person may seek a determination of the suitability of an abbreviated application for a product that the person believes is similar or related to a drug product that has been declared to be suitable for an abbreviated application. Extension of the finding that a drug product is safe and effective to another product will ordinarily be limited to other dosage forms for the same route of administration or to closely related ingredients. If preclinical or clinical evidence is needed to support the safety, or if clinical evidence is needed to support the effectiveness, of the proposed product, then an abbreviated application is not appropriate for the similar or related drug product.

(2) A person seeking a determination that an abbreviated application is suitable for a similar or related drug product shall use the petition procedures established in § 10.30. The petitioner shall set forth the reasons that justify extending the finding that an abbreviated application is suitable for one product to the similar or related product proposed to be marketed.

(3) An application submitted in the form of an abbreviated application for a drug product that has not been the subject of a finding that allows an abbreviated application for the product will be considered to be a petition under § 10.30 and will be processed as such.

(e) Each abbreviated application is required to contain a reference to FDA's finding that an abbreviated application is suitable for the specific product that is the subject of the application and to contain both an archival and a review copy of the application.

(1) The applicant shall submit a complete archival copy of the application that contains the information required under § 314.50 (a), (b), (d)(1) and (3), (e), and (g). An applicant may submit the archival copy of the application on microfiche or, if FDA agrees, another suitable microform system.

(2) The applicant shall submit a review copy that contains the technical sections described in § 314.50(d)(1) and (3). Each of the technical sections in the review copy is required to be separately bound with a copy of the application form required under § 314.50(a).

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

(Collection of information requirements approved by the Office of Management and Budget under number 0910-0001)

[50 FR 7493, Feb. 22, 1985, as amended at 50 FR 21238, May 23, 1985]

§ 314.56 Drug products for which abbreviated applications are suitable.

Abbreviated applications are suitable for the following drugs within the limits set forth in § 314.55(c):

(a) Duplicates of drug products that were first approved before October 10, 1962, and reformulations of these products, if the original or reformulated product has been evaluated as part of the drug efficacy study and announced by notice in the FEDERAL REGISTER as effective for one or more indi-

cations, and if the Food and Drug Administration has made a finding that an abbreviated application is suitable.

(b) [Reserved]

(c) Drug products that are very closely related to a product described in paragraph (a) of this section and that are subject to a separate finding of suitability for marketing under an abbreviated application.

(d) Drug products that contain a chlorofluorocarbon determined to be an essential use and identified in § 2.125(h)(2) as suitable for an abbreviated application.

(e) Duplicates of an antibiotic drug for which FDA has approved an application.

§ 314.60 Amendments to an unapproved application.

The applicant may submit an amendment to an application that is filed under § 314.100, but not yet approved. The submission of a major amendment (for example, an amendment that contains significant new data from a previously unreported study or detailed new analyses of previously submitted data), whether on the applicant's own initiative or at the invitation of the agency, constitutes an agreement by the applicant under section 505(c) of the act to extend the date by which the agency is required to reach a decision on the application. Ordinarily, the agency will extend the review period for a major amendment but only for the time necessary to review the new information. However, the agency may not extend the review period more than 180 days. If the agency extends the review period for the application, the director of the division responsible for reviewing the application will notify the applicant of the length of the extension. The submission of an amendment that is not a major amendment will not extend the review period.

§ 314.65 Withdrawal by the applicant of an unapproved application.

An applicant may at any time withdraw an application that is not yet approved by notifying the Food and Drug Administration in writing. The agency will consider an applicant's failure to respond within 10 days to an approvable letter under § 314.110 or a not approvable letter under § 314.120 to be a request by the applicant to withdraw the application. A decision to withdraw the application is without prejudice to refiling. The agency will retain the application and will provide a copy to the applicant on request under the fee schedule in § 20.42 of FDA's public information regulations.

§ 314.70 Supplements and other changes to an approved application.

(a) *Changes to an approved application.* The applicant shall notify the Food and Drug Administration 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 shall notify FDA about it in a supplemental application 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. Notwithstanding the requirements of paragraphs (b) and (c) of this section, an applicant shall make a change provided for in those paragraphs (for example, the deletion of an ingredient common to many drug products) in accordance with a guideline, notice, or regulation published in the FEDERAL REGISTER that provides for a less burdensome notification of the change (for example, by notification at the time a supplement is submitted or in the next annual report).

(b) *Supplements requiring FDA approval before the change is made.* An applicant shall submit a supplement, and obtain FDA approval of it, before making the changes listed below in the conditions in an approved application, unless the change is made to comply with an official compendium. An applicant may ask FDA to expedite its review of a supplement 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: "Supplement—Expedited Review Requested."