

record. In any case in which the Commissioner enters an order without a hearing under §314.200(g), the record certified by the Commissioner is required to include the requests for hearing together with the data and information submitted and the Commissioner's findings and conclusion.

(b) A manufacturer or distributor of an identical, related, or similar drug product under §310.6 may seek judicial review of an order withdrawing approval of a new drug application, whether or not a hearing has been held, in a United States court of appeals under section 505(h) of the act.

Subpart F—Administrative Procedures for Antibiotics

SOURCE: 50 FR 7493, Feb. 22, 1985, unless otherwise noted. Redesignated at 57 FR 17983, Apr. 28, 1992.

§314.300 Procedure for the issuance, amendment, or repeal of regulations.

(a) The procedures in part 10 apply to the issuance, amendment, or repeal of regulations under section 507 of the act.

(b)(1) The Commissioner of Food and Drugs, on his or her own initiative or on the application or request of any interested person, may publish in the FEDERAL REGISTER a notice of proposed rulemaking and order to issue, amend, or repeal any regulation contemplated by section 507 of the act. The notice and order may be general (that is, simply summarizing in a general way the information resulting in the notice and order) or specific (that is, either referring to specific requirements in the statute and regulations with which there is a lack of compliance, or providing a detailed description and analysis of the specific facts resulting in the notice and order).

(2) The Food and Drug Administration will give interested persons an opportunity to submit written comments and to request an informal conference on the proposal, unless the notice and opportunity for comment and informal conference have already been provided in connection with the announcement of the reports of the National Academy of Sciences/National Research Council,

Drug Efficacy Study Group, to persons who will be adversely affected, or as provided in §§10.40(e) and 12.20(c)(2). A person is required to request an informal conference within 30 days of the notice of proposed rulemaking unless otherwise specified in the notice. If an informal conference is requested and granted, those persons participating in the conference may submit comments, within 30 days of the conference, unless otherwise specified in the proposal.

(3) It is the responsibility of every manufacturer and distributor of an antibiotic drug product to review every proposal published in the FEDERAL REGISTER to determine whether it covers any drug product that person manufactures or distributes.

(4) After considering the written comments, the results of any conference, and the data available, the Commissioner will publish an order in the FEDERAL REGISTER acting on the proposal, with an opportunity for any person who will be adversely affected to file objections, to request a hearing, and to show reasonable grounds for the hearing. Any person who wishes to participate in a hearing, shall file with the Dockets Management Branch (HFA-305), Food and Drug Administration, rm. 1-23, 12420 Parklawn Dr., Rockville, MD 20857, (i) within 30 days after the date of the publication of the order a written notice of participation and request for a hearing and (ii) within 60 days after the date of publication of the order, unless a different period of time is specified in the order, the studies on which the person relies to justify a hearing as specified in paragraph (b)(6) of this section. The person may incorporate by reference the raw data underlying a study if the data were previously submitted to FDA as part of an application or other report.

(5) FDA will not consider data or analysis submitted after 60 days in determining whether a hearing is warranted unless they are derived from well-controlled studies begun before the date of the order and the results of the studies were not available within 60 days after the date of publication of the order. Nevertheless, FDA may consider other studies on the basis of a showing by the person requesting a hearing of inadvertent omission and

hardship. The person requesting a hearing shall list in the request for hearing all studies in progress, the results of which the person intends later to submit in support of the request for hearing. The person shall submit under paragraph (b)(4)(ii) of this section a copy of the complete protocol, a list of the participating investigators, and a brief status report of the studies.

(6) The person requesting a hearing is required to submit as required under § 314.200(c)(1)(ii) the studies (including all protocols and underlying raw data) on which the person relies to justify a hearing with respect to the drug product. A financial certification or disclosure statement or both as required by part 54 of this chapter must accompany all clinical data submitted with the request for hearing. Except, a person who requests a hearing on a proposal is not required to submit additional studies and analyses if the studies upon which the person relies have been submitted in an application and in the format and containing the summaries required under § 314.50.

(i) If the grounds for FDA proposed action concern the effectiveness of the drug, each request for hearing is required to be supported only by adequate and well-controlled clinical studies meeting all of the precise requirements of § 314.126 and, for combination drug products, § 300.50, or by other studies not meeting those requirements for which a waiver has been previously granted by FDA under § 314.126. Each person requesting a hearing shall submit all adequate and well-controlled clinical studies on the drug product, any unfavorable analyses, views, or judgments with respect to the studies. No other data, information, or studies may be submitted.

(ii) The submission is required to include a factual analysis of all the studies submitted. If the grounds for FDA proposed action concern the effectiveness of the drug, the analysis is required to specify how each study accords, on a point-by-point basis, with each criterion required for an adequate well-controlled clinical investigation established under § 314.126 and, if the product is a combination drug product, with each of the requirements for a combination drug established in

§ 300.50, or the study is required to be accompanied by an appropriate waiver previously granted by FDA. If a study concerns a drug entity or dosage form or condition of use or mode of administration other than the one in question, that fact is required to be clearly stated. Any study conducted on the final marketed form of the drug product is required to be clearly identified.

(iii) Each person requesting a hearing shall submit an analysis of the data upon which the person relies, except that the required information relating either to safety or to effectiveness may be omitted if the notice of opportunity for hearing does not raise any issue with respect to that aspect of the drug; information on compliance with § 300.50 may be omitted if the drug product is not a combination drug product. FDA can most efficiently consider submissions made in the following format.

- I. Safety data.
 - A. Animal safety data.
 1. Individual active components.
 - a. Controlled studies.
 - b. Partially controlled or uncontrolled studies.
 2. Combinations of the individual active components.
 - a. Controlled studies.
 - b. Partially controlled or uncontrolled studies.
 - B. Human safety data.
 1. Individual active components.
 - a. Controlled studies.
 - b. Partially controlled or uncontrolled studies.
 - c. Documented case reports.
 - d. Pertinent marketing experiences that may influence a determination about the safety of each individual active component.
 2. Combinations of the individual active components.
 - a. Controlled studies.
 - b. Partially controlled or uncontrolled studies.
 - c. Documented case reports.
 - d. Pertinent marketing experiences that may influence a determination about the safety of each individual active component.
- II. Effectiveness data.
 - A. Individual active components: Controlled studies, with an analysis showing clearly how each study satisfies, on a point-by-point basis, each of the criteria required by § 314.126.
 - B. Combinations of individual active components.
 1. Controlled studies with an analysis showing clearly how each study satisfies on

a point-by-point basis, each of the criteria required by §314.126.

2. An analysis showing clearly how each requirement of §300.50 has been satisfied.

III. A summary of the data and views setting forth the medical rationale and purpose for the drug and its ingredients and the scientific basis for the conclusion that the drug and its ingredients have been proven safe and/or effective for the intended use. If there is an absence of controlled studies in the material submitted or the requirements of any element of §300.50 or §314.126 have not been fully met, that fact is required to be stated clearly and a waiver obtained under §314.126 is required to be submitted.

IV. A statement signed by the person responsible for such submission that it includes in full (or incorporates by reference as permitted in §314.200(c)(2)) all studies and information specified in §314.200(d).

(WARNING: A willfully false statement is a criminal offense, 18 U.S.C. 1001.)

(7) *Separation of functions.* Separation of functions commences upon receipt of a request for hearing. The Director of the Center for Drug Evaluation and Research will prepare an analysis of the request and a proposed order ruling on the matter. The analysis and proposed order, the request for hearing, and any proposed order denying a hearing and response under paragraph (b)(8) (ii) or (iii) of this section will be submitted to the Office of the Commissioner for review and decision. When the Center for Drug Evaluation and Research recommends denial of a hearing on all issues on which a hearing is requested, no representative of the Center will participate or advise in the review and decision by the Commissioner. When the Center for Drug Evaluation and Research recommends that a hearing be granted on one or more issues on which a hearing is requested, separation of functions terminates as to those issues, and representatives of the Center may participate or advise in the review and decision by the Commissioner on those issues. The Commissioner may modify the text of the issues, but may not deny a hearing on those issues. Separation of functions continues with respect to issues on which the Center for Drug Evaluation and Research has recommended denial of a hearing. The Commissioner will neither evaluate nor rule on the Center's recommendation on such issues and such issues will not be included in the notice of hear-

ing. Participants in the hearing may make a motion to the presiding officer for the inclusion of any such issue in the hearing. The ruling on such a motion is subject to review in accordance with §12.35(b). Failure to so move constitutes a waiver of the right to a hearing on such an issue. Separation of functions on all issues resumes upon issuance of a notice of hearing. The Office of the General Counsel, Department of Health and Human Services, will observe the same separation of functions.

(8) *Summary judgment.* A person who requests a hearing may not rely upon allegations or denials but is required to set forth specific facts showing that there is a genuine and substantial issue of fact that requires a hearing with respect to a particular drug product specified in the request for hearing.

(i) Where a specific notice of opportunity for hearing (as defined in paragraph (b)(1) of this section) is used, the Commissioner will enter summary judgment against a person who requests a hearing, making findings and conclusions, denying a hearing, if it conclusively appears from the face of the data, information, and factual analyses in the request for the hearing that there is no genuine and substantial issue of fact which precludes the refusal to approve the application or the withdrawal of approval of the application; for example, no adequate and well-controlled clinical investigations meeting each of the precise elements of §314.126 and, for a combination drug product, §300.50, showing effectiveness have been identified. Any order entering summary judgment is required to set forth the Commissioner's findings and conclusions in detail and is required to specify why each study submitted fails to meet the requirements of the statute and regulations or why the request for hearing does not raise a genuine and substantial issue of fact.

(ii) When following a general notice of opportunity for a hearing (as defined in paragraph (b)(1) of this section) the Director of the Center for Drug Evaluation and Research concludes that summary judgment against a person requesting a hearing should be considered, the Director will serve upon the

person requesting a hearing by registered mail a proposed order denying a hearing. This person has 60 days after receipt of the proposed order to respond with sufficient data, information, and analyses to demonstrate that there is a genuine and substantial issue of fact which justifies a hearing.

(iii) When following a general or specific notice of opportunity for a hearing a person requesting a hearing submits data or information of a type required by the statute and regulations, and the Director of the Center for Drug Evaluation and Research concludes that summary judgment against the person should be considered, the Director will serve upon the person by registered mail a proposed order denying a hearing. The person has 60 days after receipt of the proposed order to respond with sufficient data, information, and analyses to demonstrate that there is a genuine and substantial issue of fact which justifies a hearing.

(iv) If review of the data, information, and analyses submitted show that the basis for the order is not valid, for example, that substantial evidence of effectiveness exists, the Commissioner will enter summary judgment for the person requesting the hearing, and revoke the order. If a hearing is not requested, the order will become effective as published.

(v) If the Commissioner grants a hearing, it will be conducted under part 12.

(vi) The Commissioner will grant a hearing if there exists a genuine and substantial issue of fact or if the Commissioner concludes that a hearing would otherwise be in the public interest.

(9) The repeal of any regulation constitutes a revocation of all outstanding certificates based upon such regulation. However, the Commissioner may, in his or her discretion, defer or stay such action pending a ruling on any related request for a hearing or pending any related hearing or other administrative or judicial proceeding.

(c) Whenever any interested person submits an application or request under section 507 of the act and part 314 and FDA sends the person an approvable letter under §314.110 or a not approvable letter under §314.120, the per-

son may file a petition proposing the issuance, amendment, or repeal of the regulation under the provisions of section 507(f) of the act and part 10. The Commissioner shall cause the regulation proposed in the petition to be published in the FEDERAL REGISTER within 60 days of the receipt of an acceptable petition and further proceedings shall be in accord with the provisions of sections 507(f) and 701 (f) and (g) of the act and part 10.

(d) (1) FDA will not promulgate a regulation providing for the certification of any batch of any drug composed wholly or in part of any kind of penicillin, streptomycin, chlortetracycline, chloramphenicol, bacitracin, or any other antibiotic drug, or any derivative thereof, intended for human use and no existing regulation will be continued in effect unless it is established by substantial evidence that the drug will have such characteristics of identity, strength, quality, and purity necessary to adequately ensure safety and efficacy of use. "Substantial evidence" has been defined by Congress to mean "evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions prescribed, recommended, or suggested in the labeling or proposed labeling thereof." This definition is made applicable to a number of antibiotic drugs by section 507(h) of the act and it is the test of efficacy that FDA will apply in promulgating, amending, or repealing regulations for all antibiotics under section 507(a) of the act as well.

(2) The scientific essentials of an adequate and well-controlled clinical investigation are described in §314.126.

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

[50 FR 7493, Feb. 22, 1985; 50 FR 14212, Apr. 11, 1985, as amended at 50 FR 21238, May 23, 1985; 55 FR 11580, Mar. 29, 1990; 59 FR 14365, Mar. 28, 1994; 63 FR 5252, Feb. 2, 1998]

EFFECTIVE DATE NOTE: At 63 FR 5252, Feb. 2, 1998, §314.300 was amended in the introductory text of paragraph (b)(6) by adding a new sentence after the first sentence, effective Feb. 2, 1999.

Subpart G—Miscellaneous Provisions

SOURCE: 50 FR 7493, Feb. 22, 1985, unless otherwise noted. Redesignated at 57 FR 17983, Apr. 28, 1992.

§314.410 Imports and exports of new drugs and antibiotics.

(a) *Imports.* (1) A new drug or an antibiotic may be imported into the United States if: (i) It is the subject of an approved application under this part or, in the case of an antibiotic not exempt from certification under part 433, it is also certified or released; or (ii) it complies with the regulations pertaining to investigational new drugs under part 312; and it complies with the general regulations pertaining to imports under subpart E of part 1.

(2) A drug substance intended for use in the manufacture, processing, or re-packing of a new drug may be imported into the United States if it complies with the labeling exemption in §201.122 pertaining to shipments of drug substances in domestic commerce.

(b) *Exports.* (1) A new drug or an antibiotic may be exported if it is the subject of an approved application under this part, and, in the case of an antibiotic, it is certified or released, or it complies with the regulations pertaining to investigational new drugs under part 312.

(2) A new drug substance that is covered by an application approved under this part for use in the manufacture of an approved drug product may be exported by the applicant or any person listed as a supplier in the approved application, provided the drug substance intended for export meets the specifications of, and is shipped with a copy of the labeling required for, the approved drug product.

(3) An antibiotic drug product or drug substance that is subject to certification under section 507 of the act, but which has not been certified or released, may be exported under section 801(e) of the act if it meets the following conditions:

(i) It meets the specifications of the foreign purchaser;

(ii) It is not in conflict with the laws of the country to which it is intended for export;

(iii) It is labeled on the outside of the shipping package that it is intended for export; and

(iv) It is not sold or offered for sale in the United States.

§314.420 Drug master files.

(a) A drug master file is a submission of information to the Food and Drug Administration by a person (the drug master file holder) who intends it to be used for one of the following purposes: To permit the holder to incorporate the information by reference when the holder submits an investigational new drug application under part 312 or submits an application or an abbreviated application or an amendment or supplement to them under this part, or to permit the holder to authorize other persons to rely on the information to support a submission to FDA without the holder having to disclose the information to the person. FDA ordinarily neither independently reviews drug master files nor approves or disapproves submissions to a drug master file. Instead, the agency customarily reviews the information only in the context of an application under part 312 or this part. A drug master file may contain information of the kind required for any submission to the agency, including information about the following:

(1) Manufacturing site, facilities, operating procedures, and personnel (because an FDA on-site inspection of a foreign drug manufacturing facility presents unique problems of planning and travel not presented by an inspection of a domestic manufacturing facility, this information is only recommended for foreign manufacturing establishments);

(2) Drug substance, drug substance intermediate, and materials used in their preparation, or drug product;

(3) Packaging materials;

(4) Excipient, colorant, flavor, essence, or materials used in their preparation;