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TITLE 21--FOOD AND DRUGS

CHAPTER 9--FEDERAL FOOD, DRUG, AND COSMETIC ACT

SUBCHAPTER V--DRUGS AND DEVICES

Part A--Drugs and Devices

Sec. 355. New drugs

(a) Necessity of effective approval of application

No person shall introduce or deliver for introduction into interstate commerce any new drug, unless an approval of an application filed pursuant to subsection (b) or (j) of this section is effective with respect to such drug.

(b) Filing application; contents

(1) Any person may file with the Secretary an application with respect to any drug subject to the provisions of subsection (a) of this section. Such person shall submit to the Secretary as a part of the application (A) full reports of investigations which have been made to show whether or not such drug is safe for use and whether such drug is effective in use; (B) a full list of the articles used as components of such drug; (C) a full statement of the composition of such drug; (D) a full description of the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of such drug; (E) such samples of such drug and of the articles used as components thereof as the Secretary may require; and (F) specimens of the labeling proposed to be used for such drug. The applicant shall file with the application the patent number and the expiration date of any patent which claims the drug for which the applicant submitted the application or which claims a method of using such drug and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner engaged in the manufacture, use, or sale of the drug. If an application is filed under this subsection for a drug and a patent which claims such drug or a method of using such drug is issued after the filing date but before approval of the application, the applicant shall amend the application to include the information required by the preceding sentence. Upon approval of the application, the Secretary shall publish information submitted under the two preceding sentences. The Secretary shall, in consultation with the Director of the National Institutes of Health and with representatives of the drug manufacturing industry, review and develop guidance, as appropriate, on the inclusion of women and minorities in clinical trials required by clause (A).

(2) An application submitted under paragraph (1) for a drug for which the investigations described in clause (A) of such paragraph 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 shall also include--

(A) a certification, in the opinion of the applicant and to the best of his knowledge, with respect to each patent which claims the drug for which such investigations were conducted or which claims a use for such drug for which the applicant is seeking approval under this subsection and for which information is required to be filed under paragraph (1) or subsection (c) of this section--

- (i) that such patent information has not been filed,
- (ii) that such patent has expired,
- (iii) of the date on which such patent will expire, or
- (iv) that such patent is invalid or will not be infringed by the manufacture, use, or sale of the new drug for which the application is submitted; and

(B) if with respect to the drug for which investigations described in paragraph (1) (A) were conducted information was filed under paragraph (1) or subsection (c) of this section for a method of use patent which does not claim a use for which the applicant is seeking approval under this subsection, a statement that the method of use patent does not claim such a use.

(3) (A) An applicant who makes a certification described in paragraph (2) (A) (iv) shall include in the application a statement that the applicant will give the notice required by subparagraph (B) to--

- (i) each owner of the patent which is the subject of the certification or the representative of such owner designated to receive such notice, and
- (ii) the holder of the approved application under subsection (b) of this section for the drug which is claimed by the patent or a use of which is claimed by the patent or the representative of such holder designated to receive such notice.

(B) The notice referred to in subparagraph (A) shall state that an application has been submitted under this subsection for the drug with respect to which the certification is made to obtain approval to engage in the commercial manufacture, use, or sale of the drug before the expiration of the patent referred to in the certification. Such notice shall include a detailed statement of the factual and legal basis of the applicant's opinion that the patent is not valid or will not be infringed.

(C) If an application is amended to include a certification described in paragraph (2) (A) (iv), the notice required by subparagraph (B) shall be given when the amended application is submitted.

(4) (A) The Secretary shall issue guidance for the individuals who review applications submitted under paragraph (1) or under section 262 of title 42, which shall relate to promptness in conducting the review, technical excellence, lack of bias and conflict of interest, and knowledge of regulatory and scientific standards, and which shall apply equally to all individuals who review such applications.

(B) The Secretary shall meet with a sponsor of an investigation or an applicant for approval for a drug under this subsection or section 262 of title 42 if the sponsor or applicant makes a reasonable written request for a meeting for the purpose of reaching agreement on the design and size of clinical trials intended to form the primary basis of an effectiveness claim. The sponsor or applicant shall provide information necessary for discussion and agreement on the design and size of the clinical trials. Minutes of any such meeting shall be prepared by the Secretary and made available to the sponsor or applicant upon request.

(C) Any agreement regarding the parameters of the design and size of

clinical trials of a new drug under this paragraph that is reached between the Secretary and a sponsor or applicant shall be reduced to writing and made part of the administrative record by the Secretary. Such agreement shall not be changed after the testing begins, except--

- (i) with the written agreement of the sponsor or applicant; or
- (ii) pursuant to a decision, made in accordance with subparagraph (D) by the director of the reviewing division, that a substantial scientific issue essential to determining the safety or effectiveness of the drug has been identified after the testing has begun.

(D) A decision under subparagraph (C) (ii) by the director shall be in writing and the Secretary shall provide to the sponsor or applicant an opportunity for a meeting at which the director and the sponsor or applicant will be present and at which the director will document the scientific issue involved.

(E) The written decisions of the reviewing division shall be binding upon, and may not directly or indirectly be changed by, the field or compliance division personnel unless such field or compliance division personnel demonstrate to the reviewing division why such decision should be modified.

(F) No action by the reviewing division may be delayed because of the unavailability of information from or action by field personnel unless the reviewing division determines that a delay is necessary to assure the marketing of a safe and effective drug.

(G) For purposes of this paragraph, the reviewing division is the division responsible for the review of an application for approval of a drug under this subsection or section 262 of title 42 (including all scientific and medical matters, chemistry, manufacturing, and controls).

(c) Period for approval of application; period for, notice, and expedition of hearing; period for issuance of order

(1) Within one hundred and eighty days after the filing of an application under subsection (b) of this section, or such additional period as may be agreed upon by the Secretary and the applicant, the Secretary shall either--

(A) approve the application if he then finds that none of the grounds for denying approval specified in subsection (d) of this section applies, or

(B) give the applicant notice of an opportunity for a hearing before the Secretary under subsection (d) of this section on the question whether such application is approvable. If the applicant elects to accept the opportunity for hearing by written request within thirty days after such notice, such hearing shall commence not more than ninety days after the expiration of such thirty days unless the Secretary and the applicant otherwise agree. Any such hearing shall thereafter be conducted on an expedited basis and the Secretary's order thereon shall be issued within ninety days after the date fixed by the Secretary for filing final briefs.

(2) If the patent information described in subsection (b) of this section could not be filed with the submission of an application under subsection (b) of this section because the application was filed before the patent information was required under subsection (b) of this section or a patent was issued after the application was approved under such subsection, the holder of an approved application shall file with the Secretary the patent number and the expiration date of any patent which claims the drug for which the application was submitted or which claims a method of using such drug and with respect to which a claim of patent

infringement could reasonably be asserted if a person not licensed by the owner engaged in the manufacture, use, or sale of the drug. If the holder of an approved application could not file patent information under subsection (b) of this section because it was not required at the time the application was approved, the holder shall file such information under this subsection not later than thirty days after September 24, 1984, and if the holder of an approved application could not file patent information under subsection (b) of this section because no patent had been issued when an application was filed or approved, the holder shall file such information under this subsection not later than thirty days after the date the patent involved is issued. Upon the submission of patent information under this subsection, the Secretary shall publish it.

(3) The approval of an application filed under subsection (b) of this section which contains a certification required by paragraph (2) of such subsection shall be made effective on the last applicable date determined under the following:

(A) If the applicant only made a certification described in clause (i) or (ii) of subsection (b) (2) (A) of this section or in both such clauses, the approval may be made effective immediately.

(B) If the applicant made a certification described in clause (iii) of subsection (b) (2) (A) of this section, the approval may be made effective on the date certified under clause (iii).

(C) If the applicant made a certification described in clause (iv) of subsection (b) (2) (A) of this section, the approval shall be made effective immediately unless an action is brought for infringement of a patent which is the subject of the certification before the expiration of forty-five days from the date the notice provided under paragraph (3) (B) is received. If such an action is brought before the expiration of such days, the approval may be made effective upon the expiration of the thirty-month period beginning on the date of the receipt of the notice provided under paragraph (3) (B) or such shorter or longer period as the court may order because either party to the action failed to reasonably cooperate in expediting the action, except that--

(i) if before the expiration of such period the court decides that such patent is invalid or not infringed, the approval may be made effective on the date of the court decision,

(ii) if before the expiration of such period the court decides that such patent has been infringed, the approval may be made effective on such date as the court orders under section 271(e) (4) (A) of title 35, or

(iii) if before the expiration of such period the court grants a preliminary injunction prohibiting the applicant from engaging in the commercial manufacture or sale of the drug until the court decides the issues of patent validity and infringement and if the court decides that such patent is invalid or not infringed, the approval shall be made effective on the date of such court decision.

In such an action, each of the parties shall reasonably cooperate in expediting the action. Until the expiration of forty-five days from the date the notice made under paragraph (3) (B) is received, no action may be brought under section 2201 of title 28 for a declaratory judgment with respect to the patent. Any action brought under such section 2201 shall be brought in the judicial district where the defendant has its principal place of business or a regular and established place of business.

(D) (i) If an application (other than an abbreviated new drug

application) submitted under subsection (b) of this section for a drug, no active ingredient (including any ester or salt of the active ingredient) of which has been approved in any other application under subsection (b) of this section, was approved during the period beginning January 1, 1982, and ending on September 24, 1984, the Secretary may not make the approval of another application for a drug for which the investigations described in clause (A) of subsection (b)(1) of this section 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 effective before the expiration of ten years from the date of the approval of the application previously approved under subsection (b) of this section.

(ii) If an application submitted under subsection (b) of this section for a drug, no active ingredient (including any ester or salt of the active ingredient) of which has been approved in any other application under subsection (b) of this section, is approved after September 24, 1984, no application which refers to the drug for which the subsection (b) application was submitted and for which the investigations described in clause (A) of subsection (b)(1) of this section 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 may be submitted under subsection (b) of this section before the expiration of five years from the date of the approval of the application under subsection (b) of this section, except that such an application may be submitted under subsection (b) of this section after the expiration of four years from the date of the approval of the subsection (b) application if it contains a certification of patent invalidity or noninfringement described in clause (iv) of subsection (b)(2)(A) of this section. The approval of such an application shall be made effective in accordance with this paragraph except that, if an action for patent infringement is commenced during the one-year period beginning forty-eight months after the date of the approval of the subsection (b) application, the thirty-month period referred to in subparagraph (C) shall be extended by such amount of time (if any) which is required for seven and one-half years to have elapsed from the date of approval of the subsection (b) application.

(iii) If an application submitted under subsection (b) of this section for a drug, which includes an active ingredient (including any ester or salt of the active ingredient) that has been approved in another application approved under subsection (b) of this section, is approved after September 24, 1984, and if such application contains reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant, the Secretary may not make the approval of an application submitted under subsection (b) of this section for the conditions of approval of such drug in the approved subsection (b) application effective before the expiration of three years from the date of the approval of the application under subsection (b) of this section if the investigations described in clause (A) of subsection (b)(1) of this section and relied upon by the applicant for approval of the application were not conducted by or for the applicant and if the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted.

(iv) If a supplement to an application approved under subsection (b) of this section is approved after September 24, 1984, and the

supplement contains reports of new clinical investigations (other than bioavailability \1\ studies) essential to the approval of the supplement and conducted or sponsored by the person submitting the supplement, the Secretary may not make the approval of an application submitted under subsection (b) of this section for a change approved in the supplement effective before the expiration of three years from the date of the approval of the supplement under subsection (b) of this section if the investigations described in clause (A) of subsection (b)(1) of this section and relied upon by the applicant for approval of the application were not conducted by or for the applicant and if the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted.

\1\ So in original. Probably should be ``bioavailability''.

(v) If an application (or supplement to an application) submitted under subsection (b) of this section for a drug, which includes an active ingredient (including any ester or salt of the active ingredient) that has been approved in another application under subsection (b) of this section, was approved during the period beginning January 1, 1982, and ending on September 24, 1984, the Secretary may not make the approval of an application submitted under this subsection and for which the investigations described in clause (A) of subsection (b)(1) of this section 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 and which refers to the drug for which the subsection (b) application was submitted effective before the expiration of two years from September 24, 1984.

(4) A drug manufactured in a pilot or other small facility may be used to demonstrate the safety and effectiveness of the drug and to obtain approval for the drug prior to manufacture of the drug in a larger facility, unless the Secretary makes a determination that a full scale production facility is necessary to ensure the safety or effectiveness of the drug.

(d) Grounds for refusing application; approval of application;
``substantial evidence'' defined

If the Secretary finds, after due notice to the applicant in accordance with subsection (c) of this section and giving him an opportunity for a hearing, in accordance with said subsection, that (1) the investigations, reports of which are required to be submitted to the Secretary pursuant to subsection (b) of this section, do not include adequate tests by all methods reasonably applicable to show whether or not such drug is safe for use under the conditions prescribed, recommended, or suggested in the proposed labeling thereof; (2) the results of such tests show that such drug is unsafe for use under such conditions or do not show that such drug is safe for use under such conditions; (3) the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of such drug are inadequate to preserve its identity, strength, quality, and purity; (4) upon the basis of the information submitted to him as part of the application, or upon the basis of any other information before him with respect to such drug, he has insufficient information to determine whether such drug is safe for use under such conditions; or (5) evaluated on the basis of the information submitted to him as part of

the application and any other information before him with respect to such drug, there is a lack of substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling thereof; or (6) the application failed to contain the patent information prescribed by subsection (b) of this section; or (7) based on a fair evaluation of all material facts, such labeling is false or misleading in any particular; he shall issue an order refusing to approve the application. If, after such notice and opportunity for hearing, the Secretary finds that clauses (1) through (6) do not apply, he shall issue an order approving the application. As used in this subsection and subsection (e) of this section, the term ``substantial evidence'' means 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 of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof. If the Secretary determines, based on relevant science, that data from one adequate and well-controlled clinical investigation and confirmatory evidence (obtained prior to or after such investigation) are sufficient to establish effectiveness, the Secretary may consider such data and evidence to constitute substantial evidence for purposes of the preceding sentence.

(e) Withdrawal of approval; grounds; immediate suspension upon finding imminent hazard to public health

The Secretary shall, after due notice and opportunity for hearing to the applicant, withdraw approval of an application with respect to any drug under this section if the Secretary finds (1) that clinical or other experience, tests, or other scientific data show that such drug is unsafe for use under the conditions of use upon the basis of which the application was approved; (2) that new evidence of clinical experience, not contained in such application or not available to the Secretary until after such application was approved, or tests by new methods, or tests by methods not deemed reasonably applicable when such application was approved, evaluated together with the evidence available to the Secretary when the application was approved, shows that such drug is not shown to be safe for use under the conditions of use upon the basis of which the application was approved; or (3) on the basis of new information before him with respect to such drug, evaluated together with the evidence available to him when the application was approved, that there is a lack of substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling thereof; or (4) the patent information prescribed by subsection (c) of this section was not filed within thirty days after the receipt of written notice from the Secretary specifying the failure to file such information; or (5) that the application contains any untrue statement of a material fact: Provided, That if the Secretary (or in his absence the officer acting as Secretary) finds that there is an imminent hazard to the public health, he may suspend the approval of such application immediately, and give the applicant prompt notice of his action and afford the applicant the opportunity for an expedited hearing under this subsection; but the authority conferred by this proviso to suspend the approval of an application shall not be delegated. The Secretary may also, after due notice and opportunity for hearing to the applicant, withdraw the approval of an application submitted under subsection (b) or (j) of this

section with respect to any drug under this section if the Secretary finds (1) that the applicant has failed to establish a system for maintaining required records, or has repeatedly or deliberately failed to maintain such records or to make required reports, in accordance with a regulation or order under subsection (k) of this section or to comply with the notice requirements of section 360(k)(2) of this title, or the applicant has refused to permit access to, or copying or verification of, such records as required by paragraph (2) of such subsection; or (2) that on the basis of new information before him, evaluated together with the evidence before him when the application was approved, the methods used in, or the facilities and controls used for, the manufacture, processing, and packing of such drug are inadequate to assure and preserve its identity, strength, quality, and purity and were not made adequate within a reasonable time after receipt of written notice from the Secretary specifying the matter complained of; or (3) that on the basis of new information before him, evaluated together with the evidence before him when the application was approved, the labeling of such drug, based on a fair evaluation of all material facts, is false or misleading in any particular and was not corrected within a reasonable time after receipt of written notice from the Secretary specifying the matter complained of. Any order under this subsection shall state the findings upon which it is based.

(f) Revocation of order refusing, withdrawing or suspending approval of application

Whenever the Secretary finds that the facts so require, he shall revoke any previous order under subsection (d) or (e) of this section refusing, withdrawing, or suspending approval of an application and shall approve such application or reinstate such approval, as may be appropriate.

(g) Service of orders

Orders of the Secretary issued under this section shall be served (1) in person by any officer or employee of the department designated by the Secretary or (2) by mailing the order by registered mail or by certified mail addressed to the applicant or respondent at his last-known address in the records of the Secretary.

(h) Appeal from order

An appeal may be taken by the applicant from an order of the Secretary refusing or withdrawing approval of an application under this section. Such appeal shall be taken by filing in the United States court of appeals for the circuit wherein such applicant resides or has his principal place of business, or in the United States Court of Appeals for the District of Columbia Circuit, within sixty days after the entry of such order, a written petition praying that the order of the Secretary be set aside. A copy of such petition shall be forthwith transmitted by the clerk of the court to the Secretary, or any officer designated by him for that purpose, and thereupon the Secretary shall certify and file in the court the record upon which the order complained of was entered, as provided in section 2112 of title 28. Upon the filing of such petition such court shall have exclusive jurisdiction to affirm or set aside such order, except that until the filing of the record the Secretary may modify or set aside his order. No objection to the order of the Secretary shall be considered by the court unless such objection shall have been urged before the Secretary or unless there were reasonable grounds for failure so to do. The finding of the Secretary as

to the facts, if supported by substantial evidence, shall be conclusive. If any person shall apply to the court for leave to adduce additional evidence, and shall show to the satisfaction of the court that such additional evidence is material and that there were reasonable grounds for failure to adduce such evidence in the proceeding before the Secretary, the court may order such additional evidence to be taken before the Secretary and to be adduced upon the hearing in such manner and upon such terms and conditions as to the court may seem proper. The Secretary may modify his findings as to the facts by reason of the additional evidence so taken, and he shall file with the court such modified findings which, if supported by substantial evidence, shall be conclusive, and his recommendation, if any, for the setting aside of the original order. The judgment of the court affirming or setting aside any such order of the Secretary shall be final, subject to review by the Supreme Court of the United States upon certiorari or certification as provided in section 1254 of title 28. The commencement of proceedings under this subsection shall not, unless specifically ordered by the court to the contrary, operate as a stay of the Secretary's order.

(i) Exemptions of drugs for research; discretionary and mandatory conditions; direct reports to Secretary

(1) The Secretary shall promulgate regulations for exempting from the operation of the foregoing subsections of this section drugs intended solely for investigational use by experts qualified by scientific training and experience to investigate the safety and effectiveness of drugs. Such regulations may, within the discretion of the Secretary, among other conditions relating to the protection of the public health, provide for conditioning such exemption upon--

(A) the submission to the Secretary, before any clinical testing of a new drug is undertaken, of reports, by the manufacturer or the sponsor of the investigation of such drug, of preclinical tests (including tests on animals) of such drug adequate to justify the proposed clinical testing;

(B) the manufacturer or the sponsor of the investigation of a new drug proposed to be distributed to investigators for clinical testing obtaining a signed agreement from each of such investigators that patients to whom the drug is administered will be under his personal supervision, or under the supervision of investigators responsible to him, and that he will not supply such drug to any other investigator, or to clinics, for administration to human beings;

(C) the establishment and maintenance of such records, and the making of such reports to the Secretary, by the manufacturer or the sponsor of the investigation of such drug, of data (including but not limited to analytical reports by investigators) obtained as the result of such investigational use of such drug, as the Secretary finds will enable him to evaluate the safety and effectiveness of such drug in the event of the filing of an application pursuant to subsection (b) of this section; and

(D) the submission to the Secretary by the manufacturer or the sponsor of the investigation of a new drug of a statement of intent regarding whether the manufacturer or sponsor has plans for assessing pediatric safety and efficacy.

(2) Subject to paragraph (3), a clinical investigation of a new drug may begin 30 days after the Secretary has received from the manufacturer or sponsor of the investigation a submission containing such information about the drug and the clinical investigation, including--

(A) information on design of the investigation and adequate

reports of basic information, certified by the applicant to be accurate reports, necessary to assess the safety of the drug for use in clinical investigation; and

(B) adequate information on the chemistry and manufacturing of the drug, controls available for the drug, and primary data tabulations from animal or human studies.

(3) (A) At any time, the Secretary may prohibit the sponsor of an investigation from conducting the investigation (referred to in this paragraph as a ``clinical hold'') if the Secretary makes a determination described in subparagraph (B). The Secretary shall specify the basis for the clinical hold, including the specific information available to the Secretary which served as the basis for such clinical hold, and confirm such determination in writing.

(B) For purposes of subparagraph (A), a determination described in this subparagraph with respect to a clinical hold is that--

(i) the drug involved represents an unreasonable risk to the safety of the persons who are the subjects of the clinical investigation, taking into account the qualifications of the clinical investigators, information about the drug, the design of the clinical investigation, the condition for which the drug is to be investigated, and the health status of the subjects involved; or

(ii) the clinical hold should be issued for such other reasons as the Secretary may by regulation establish (including reasons established by regulation before November 21, 1997).

(C) Any written request to the Secretary from the sponsor of an investigation that a clinical hold be removed shall receive a decision, in writing and specifying the reasons therefor, within 30 days after receipt of such request. Any such request shall include sufficient information to support the removal of such clinical hold.

(4) Regulations under paragraph (1) shall provide that such exemption shall be conditioned upon the manufacturer, or the sponsor of the investigation, requiring that experts using such drugs for investigational purposes certify to such manufacturer or sponsor that they will inform any human beings to whom such drugs, or any controls used in connection therewith, are being administered, or their representatives, that such drugs are being used for investigational purposes and will obtain the consent of such human beings or their representatives, except where it is not feasible or it is contrary to the best interests of such human beings. Nothing in this subsection shall be construed to require any clinical investigator to submit directly to the Secretary reports on the investigational use of drugs.

(j) Abbreviated new drug applications

(1) Any person may file with the Secretary an abbreviated application for the approval of a new drug.

(2) (A) An abbreviated application for a new drug shall contain--

(i) information to show that the conditions of use prescribed, recommended, or suggested in the labeling proposed for the new drug have been previously approved for a drug listed under paragraph (7) (hereinafter in this subsection referred to as a ``listed drug'');

(ii) (I) if the listed drug referred to in clause (i) has only one active ingredient, information to show that the active ingredient of the new drug is the same as that of the listed drug;

(II) if the listed drug referred to in clause (i) has more than one active ingredient, information to show that the active ingredients of the new drug are the same as those of the listed drug, or

(III) if the listed drug referred to in clause (i) has more than one active ingredient and if one of the active ingredients of the new drug is different and the application is filed pursuant to the approval of a petition filed under subparagraph (C), information to show that the other active ingredients of the new drug are the same as the active ingredients of the listed drug, information to show that the different active ingredient is an active ingredient of a listed drug or of a drug which does not meet the requirements of section 321(p) of this title, and such other information respecting the different active ingredient with respect to which the petition was filed as the Secretary may require;

(iii) information to show that the route of administration, the dosage form, and the strength of the new drug are the same as those of the listed drug referred to in clause (i) or, if the route of administration, the dosage form, or the strength of the new drug is different and the application is filed pursuant to the approval of a petition filed under subparagraph (C), such information respecting the route of administration, dosage form, or strength with respect to which the petition was filed as the Secretary may require;

(iv) information to show that the new drug is bioequivalent to the listed drug referred to in clause (i), except that if the application is filed pursuant to the approval of a petition filed under subparagraph (C), information to show that the active ingredients of the new drug are of the same pharmacological or therapeutic class as those of the listed drug referred to in clause (i) and the new drug can be expected to have the same therapeutic effect as the listed drug when administered to patients for a condition of use referred to in clause (i);

(v) information to show that the labeling proposed for the new drug is the same as the labeling approved for the listed drug referred to in clause (i) except for changes required because of differences approved under a petition filed under subparagraph (C) or because the new drug and the listed drug are produced or distributed by different manufacturers;

(vi) the items specified in clauses (B) through (F) of subsection (b) (1) of this section;

(vii) a certification, in the opinion of the applicant and to the best of his knowledge, with respect to each patent which claims the listed drug referred to in clause (i) or which claims a use for such listed drug for which the applicant is seeking approval under this subsection and for which information is required to be filed under subsection (b) or (c) of this section--

- (I) that such patent information has not been filed,
- (II) that such patent has expired,
- (III) of the date on which such patent will expire, or
- (IV) that such patent is invalid or will not be infringed by the manufacture, use, or sale of the new drug for which the application is submitted; and

(viii) if with respect to the listed drug referred to in clause (i) information was filed under subsection (b) or (c) of this section for a method of use patent which does not claim a use for which the applicant is seeking approval under this subsection, a statement that the method of use patent does not claim such a use.

The Secretary may not require that an abbreviated application contain information in addition to that required by clauses (i) through (viii).

(B) (i) An applicant who makes a certification described in subparagraph (A) (vii) (IV) shall include in the application a statement that the applicant will give the notice required by clause (ii) to--

(I) each owner of the patent which is the subject of the certification or the representative of such owner designated to receive such notice, and

(II) the holder of the approved application under subsection (b) of this section for the drug which is claimed by the patent or a use of which is claimed by the patent or the representative of such holder designated to receive such notice.

(ii) The notice referred to in clause (i) shall state that an application, which contains data from bioavailability or bioequivalence studies, has been submitted under this subsection for the drug with respect to which the certification is made to obtain approval to engage in the commercial manufacture, use, or sale of such drug before the expiration of the patent referred to in the certification. Such notice shall include a detailed statement of the factual and legal basis of the applicant's opinion that the patent is not valid or will not be infringed.

(iii) If an application is amended to include a certification described in subparagraph (A) (vii) (IV), the notice required by clause (ii) shall be given when the amended application is submitted.

(C) If a person wants to submit an abbreviated application for a new drug which has a different active ingredient or whose route of administration, dosage form, or strength differ from that of a listed drug, such person shall submit a petition to the Secretary seeking permission to file such an application. The Secretary shall approve or disapprove a petition submitted under this subparagraph within ninety days of the date the petition is submitted. The Secretary shall approve such a petition unless the Secretary finds--

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

(ii) that any drug with a different active ingredient may not be adequately evaluated for approval as safe and effective on the basis of the information required to be submitted in an abbreviated application.

(3) (A) The Secretary shall issue guidance for the individuals who review applications submitted under paragraph (1), which shall relate to promptness in conducting the review, technical excellence, lack of bias and conflict of interest, and knowledge of regulatory and scientific standards, and which shall apply equally to all individuals who review such applications.

(B) The Secretary shall meet with a sponsor of an investigation or an applicant for approval for a drug under this subsection if the sponsor or applicant makes a reasonable written request for a meeting for the purpose of reaching agreement on the design and size of bioavailability and bioequivalence studies needed for approval of such application. The sponsor or applicant shall provide information necessary for discussion and agreement on the design and size of such studies. Minutes of any such meeting shall be prepared by the Secretary and made available to the sponsor or applicant.

(C) Any agreement regarding the parameters of design and size of bioavailability and bioequivalence studies of a drug under this paragraph that is reached between the Secretary and a sponsor or applicant shall be reduced to writing and made part of the administrative record by the Secretary. Such agreement shall not be changed after the testing begins, except--

- (i) with the written agreement of the sponsor or applicant; or
- (ii) pursuant to a decision, made in accordance with

subparagraph (D) by the director of the reviewing division, that a substantial scientific issue essential to determining the safety or effectiveness of the drug has been identified after the testing has begun.

(D) A decision under subparagraph (C) (ii) by the director shall be in writing and the Secretary shall provide to the sponsor or applicant an opportunity for a meeting at which the director and the sponsor or applicant will be present and at which the director will document the scientific issue involved.

(E) The written decisions of the reviewing division shall be binding upon, and may not directly or indirectly be changed by, the field or compliance office personnel unless such field or compliance office personnel demonstrate to the reviewing division why such decision should be modified.

(F) No action by the reviewing division may be delayed because of the unavailability of information from or action by field personnel unless the reviewing division determines that a delay is necessary to assure the marketing of a safe and effective drug.

(G) For purposes of this paragraph, the reviewing division is the division responsible for the review of an application for approval of a drug under this subsection (including scientific matters, chemistry, manufacturing, and controls).

(4) Subject to paragraph (5), the Secretary shall approve an application for a drug unless the Secretary finds--

(A) the methods used in, or the facilities and controls used for, the manufacture, processing, and packing of the drug are inadequate to assure and preserve its identity, strength, quality, and purity;

(B) information submitted with the application is insufficient to show that each of the proposed conditions of use have been previously approved for the listed drug referred to in the application;

(C) (i) if the listed drug has only one active ingredient, information submitted with the application is insufficient to show that the active ingredient is the same as that of the listed drug;

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

(iii) if the listed drug has more than one active ingredient and if the application is for a drug which has an active ingredient different from the listed drug, information submitted with the application is insufficient to show--

(I) that the other active ingredients are the same as the active ingredients of the listed drug, or

(II) that the different active ingredient is an active ingredient of a listed drug or a drug which does not meet the requirements of section 321(p) of this title,

or no petition to file an application for the drug with the different ingredient was approved under paragraph (2) (C);

(D) (i) if the application is for a drug whose route of administration, dosage form, or strength of the drug is the same as the route of administration, dosage form, or strength of the listed drug referred to in the application, information submitted in the application is insufficient to show that the route of administration, dosage form, or strength is the same as that of the listed drug, or

(ii) if the application is for a drug whose route of

administration, dosage form, or strength of the drug is different from that of the listed drug referred to in the application, no petition to file an application for the drug with the different route of administration, dosage form, or strength was approved under paragraph (2) (C);

(E) if the application was filed pursuant to the approval of a petition under paragraph (2) (C), the application did not contain the information required by the Secretary respecting the active ingredient, route of administration, dosage form, or strength which is not the same;

(F) information submitted in the application is insufficient to show that the drug is bioequivalent to the listed drug referred to in the application or, if the application was filed pursuant to a petition approved under paragraph (2) (C), information submitted in the application is insufficient to show that the active ingredients of the new drug are of the same pharmacological or therapeutic class as those of the listed drug referred to in paragraph (2) (A) (i) and that the new drug can be expected to have the same therapeutic effect as the listed drug when administered to patients for a condition of use referred to in such paragraph;

(G) information submitted in the 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 application except for changes required because of differences approved under a petition filed under paragraph (2) (C) or because the drug and the listed drug are produced or distributed by different manufacturers;

(H) information submitted in the application or any other information available to the Secretary shows that (i) the inactive ingredients of the drug are unsafe for use under the conditions prescribed, recommended, or suggested in the labeling proposed for the drug, or (ii) the composition of the drug is unsafe under such conditions because of the type or quantity of inactive ingredients included or the manner in which the inactive ingredients are included;

(I) the approval under subsection (c) of this section of the listed drug referred to in the application under this subsection has been withdrawn or suspended for grounds described in the first sentence of subsection (e) of this section, the Secretary has published a notice of opportunity for hearing to withdraw approval of the listed drug under subsection (c) of this section for grounds described in the first sentence of subsection (e) of this section, the approval under this subsection of the listed drug referred to in the application under this subsection has been withdrawn or suspended under paragraph (6), or the Secretary has determined that the listed drug has been withdrawn from sale for safety or effectiveness reasons;

(J) the application does not meet any other requirement of paragraph (2) (A); or

(K) the application contains an untrue statement of material fact.

(5) (A) Within one hundred and eighty days of the initial receipt of an application under paragraph (2) or within such additional period as may be agreed upon by the Secretary and the applicant, the Secretary shall approve or disapprove the application.

(B) The approval of an application submitted under paragraph (2) shall be made effective on the last applicable date determined under the following:

(i) If the applicant only made a certification described in subclause (I) or (II) of paragraph (2) (A) (vii) or in both such

subclauses, the approval may be made effective immediately.

(ii) If the applicant made a certification described in subclause (III) of paragraph (2)(A)(vii), the approval may be made effective on the date certified under subclause (III).

(iii) If the applicant made a certification described in subclause (IV) of paragraph (2)(A)(vii), the approval shall be made effective immediately unless an action is brought for infringement of a patent which is the subject of the certification before the expiration of forty-five days from the date the notice provided under paragraph (2)(B)(i) is received. If such an action is brought before the expiration of such days, the approval shall be made effective upon the expiration of the thirty-month period beginning on the date of the receipt of the notice provided under paragraph (2)(B)(i) or such shorter or longer period as the court may order because either party to the action failed to reasonably cooperate in expediting the action, except that--

(I) if before the expiration of such period the court decides that such patent is invalid or not infringed, the approval shall be made effective on the date of the court decision,

(II) if before the expiration of such period the court decides that such patent has been infringed, the approval shall be made effective on such date as the court orders under section 271(e)(4)(A) of title 35, or

(III) if before the expiration of such period the court grants a preliminary injunction prohibiting the applicant from engaging in the commercial manufacture or sale of the drug until the court decides the issues of patent validity and infringement and if the court decides that such patent is invalid or not infringed, the approval shall be made effective on the date of such court decision.

In such an action, each of the parties shall reasonably cooperate in expediting the action. Until the expiration of forty-five days from the date the notice made under paragraph (2)(B)(i) is received, no action may be brought under section 2201 of title 28, for a declaratory judgment with respect to the patent. Any action brought under section 2201 shall be brought in the judicial district where the defendant has its principal place of business or a regular and established place of business.

(iv) If the application contains a certification described in subclause (IV) of paragraph (2)(A)(vii) and is for a drug for which a previous application has been submitted under this subsection continuing such a certification, the application shall be made effective not earlier than one hundred and eighty days after--

(I) the date the Secretary receives notice from the applicant under the previous application of the first commercial marketing of the drug under the previous application, or

(II) the date of a decision of a court in an action described in clause (iii) holding the patent which is the subject of the certification to be invalid or not infringed,

whichever is earlier.

(C) If the Secretary decides to disapprove an application, the Secretary shall give the applicant notice of an opportunity for a hearing before the Secretary on the question of whether such application is approvable. If the applicant elects to accept the opportunity for hearing by written request within thirty days after such notice, such hearing shall commence not more than ninety days after the expiration of

such thirty days unless the Secretary and the applicant otherwise agree. Any such hearing shall thereafter be conducted on an expedited basis and the Secretary's order thereon shall be issued within ninety days after the date fixed by the Secretary for filing final briefs.

(D) (i) If an application (other than an abbreviated new drug application) submitted under subsection (b) of this section for a drug, no active ingredient (including any ester or salt of the active ingredient) of which has been approved in any other application under subsection (b) of this section, was approved during the period beginning January 1, 1982, and ending on September 24, 1984, the Secretary may not make the approval of an application submitted under this subsection which refers to the drug for which the subsection (b) application was submitted effective before the expiration of ten years from the date of the approval of the application under subsection (b) of this section.

(ii) If an application submitted under subsection (b) of this section for a drug, no active ingredient (including any ester or salt of the active ingredient) of which has been approved in any other application under subsection (b) of this section, is approved after September 24, 1984, no application may be submitted under this subsection which refers to the drug for which the subsection (b) application was submitted before the expiration of five years from the date of the approval of the application under subsection (b) of this section, except that such an application may be submitted under this subsection after the expiration of four years from the date of the approval of the subsection (b) application if it contains a certification of patent invalidity or noninfringement described in subclause (IV) of paragraph (2) (A) (vii). The approval of such an application shall be made effective in accordance with subparagraph (B) except that, if an action for patent infringement is commenced during the one-year period beginning forty-eight months after the date of the approval of the subsection (b) application, the thirty-month period referred to in subparagraph (B) (iii) shall be extended by such amount of time (if any) which is required for seven and one-half years to have elapsed from the date of approval of the subsection (b) application.

(iii) If an application submitted under subsection (b) of this section for a drug, which includes an active ingredient (including any ester or salt of the active ingredient) that has been approved in another application approved under subsection (b) of this section, is approved after September 24, 1984, and if such application contains reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant, the Secretary may not make the approval of an application submitted under this subsection for the conditions of approval of such drug in the subsection (b) application effective before the expiration of three years from the date of the approval of the application under subsection (b) of this section for such drug.

(iv) If a supplement to an application approved under subsection (b) of this section is approved after September 24, 1984, and the supplement contains reports of new clinical investigations (other than bioavailability studies) essential to the approval of the supplement and conducted or sponsored by the person submitting the supplement, the Secretary may not make the approval of an application submitted under this subsection for a change approved in the supplement effective before the expiration of three years from the date of the approval of the supplement under subsection (b) of this section.

(v) If an application (or supplement to an application) submitted under subsection (b) of this section for a drug, which includes an active ingredient (including any ester or salt of the active ingredient) that has been approved in another application under subsection (b) of this section, was approved during the period beginning January 1, 1982,

and ending on September 24, 1984, the Secretary may not make the approval of an application submitted under this subsection which refers to the drug for which the subsection (b) application was submitted or which refers to a change approved in a supplement to the subsection (b) application effective before the expiration of two years from September 24, 1984.

(6) If a drug approved under this subsection refers in its approved application to a drug the approval of which was withdrawn or suspended for grounds described in the first sentence of subsection (e) of this section or was withdrawn or suspended under this paragraph or which, as determined by the Secretary, has been withdrawn from sale for safety or effectiveness reasons, the approval of the drug under this subsection shall be withdrawn or suspended--

(A) for the same period as the withdrawal or suspension under subsection (e) of this section or this paragraph, or

(B) if the listed drug has been withdrawn from sale, for the period of withdrawal from sale or, if earlier, the period ending on the date the Secretary determines that the withdrawal from sale is not for safety or effectiveness reasons.

(7) (A) (i) Within sixty days of September 24, 1984, the Secretary shall publish and make available to the public--

(I) a list in alphabetical order of the official and proprietary name of each drug which has been approved for safety and effectiveness under subsection (c) of this section before September 24, 1984;

(II) the date of approval if the drug is approved after 1981 and the number of the application which was approved; and

(III) whether in vitro or in vivo bioequivalence studies, or both such studies, are required for applications filed under this subsection which will refer to the drug published.

(ii) Every thirty days after the publication of the first list under clause (i) the Secretary shall revise the list to include each drug which has been approved for safety and effectiveness under subsection (c) of this section or approved under this subsection during the thirty-day period.

(iii) When patent information submitted under subsection (b) or (c) of this section respecting a drug included on the list is to be published by the Secretary, the Secretary shall, in revisions made under clause (ii), include such information for such drug.

(B) A drug approved for safety and effectiveness under subsection (c) of this section or approved under this subsection shall, for purposes of this subsection, be considered to have been published under subparagraph (A) on the date of its approval or September 24, 1984, whichever is later.

(C) If the approval of a drug was withdrawn or suspended for grounds described in the first sentence of subsection (e) of this section or was withdrawn or suspended under paragraph (6) or if the Secretary determines that a drug has been withdrawn from sale for safety or effectiveness reasons, it may not be published in the list under subparagraph (A) or, if the withdrawal or suspension occurred after its publication in such list, it shall be immediately removed from such list--

(i) for the same period as the withdrawal or suspension under subsection (e) of this section or paragraph (6), or

(ii) if the listed drug has been withdrawn from sale, for the period of withdrawal from sale or, if earlier, the period ending on the date the Secretary determines that the withdrawal from sale is not for safety or effectiveness reasons.

A notice of the removal shall be published in the Federal Register.

(8) For purposes of this subsection:

(A) The term ``bioavailability'' means the rate and extent to which the active ingredient or therapeutic ingredient is absorbed from a drug and becomes available at the site of drug action.

(B) A drug shall be considered to be bioequivalent to a listed drug if--

(i) the rate and extent of absorption of the drug do not show a significant difference from the rate and extent of absorption of the listed drug when administered at the same molar dose of the therapeutic ingredient under similar experimental conditions in either a single dose or multiple doses; or

(ii) the extent of absorption of the drug does not show a significant difference from the extent of absorption of the listed drug when administered at the same molar dose of the therapeutic ingredient under similar experimental conditions in either a single dose or multiple doses and the difference from the listed drug in the rate of absorption of the drug is intentional, is reflected in its proposed labeling, is not essential to the attainment of effective body drug concentrations on chronic use, and is considered medically insignificant for the drug.

(9) The Secretary shall, with respect to each application submitted under this subsection, maintain a record of--

(A) the name of the applicant,

(B) the name of the drug covered by the application,

(C) the name of each person to whom the review of the chemistry of the application was assigned and the date of such assignment, and

(D) the name of each person to whom the bioequivalence review for such application was assigned and the date of such assignment.

The information the Secretary is required to maintain under this paragraph with respect to an application submitted under this subsection shall be made available to the public after the approval of such application.

(k) Records and reports; required information; regulations and orders; access to records

(1) In the case of any drug for which an approval of an application filed under subsection (b) or (j) of this section is in effect, the applicant shall establish and maintain such records, and make such reports to the Secretary, of data relating to clinical experience and other data or information, received or otherwise obtained by such applicant with respect to such drug, as the Secretary may by general regulation, or by order with respect to such application, prescribe on the basis of a finding that such records and reports are necessary in order to enable the Secretary to determine, or facilitate a determination, whether there is or may be ground for invoking subsection (e) of this section. Regulations and orders issued under this subsection and under subsection (i) of this section shall have due regard for the professional ethics of the medical profession and the interests of patients and shall provide, where the Secretary deems it to be appropriate, for the examination, upon request, by the persons to whom such regulations or orders are applicable, of similar information received or otherwise obtained by the Secretary.

(2) Every person required under this section to maintain records,

and every person in charge or custody thereof, shall, upon request of an officer or employee designated by the Secretary, permit such officer or employee at all reasonable times to have access to and copy and verify such records.

(l) Public disclosure of safety and effectiveness data

Safety and effectiveness data and information which has been submitted in an application under subsection (b) of this section for a drug and which has not previously been disclosed to the public shall be made available to the public, upon request, unless extraordinary circumstances are shown--

- (1) if no work is being or will be undertaken to have the application approved,
- (2) if the Secretary has determined that the application is not approvable and all legal appeals have been exhausted,
- (3) if approval of the application under subsection (c) of this section is withdrawn and all legal appeals have been exhausted,
- (4) if the Secretary has determined that such drug is not a new drug, or
- (5) upon the effective date of the approval of the first application under subsection (j) of this section which refers to such drug or upon the date upon which the approval of an application under subsection (j) of this section which refers to such drug could be made effective if such an application had been submitted.

(m) ``Patent'' defined

For purposes of this section, the term ``patent'' means a patent issued by the United States Patent and Trademark Office.

(n) Scientific advisory panels

(1) For the purpose of providing expert scientific advice and recommendations to the Secretary regarding a clinical investigation of a drug or the approval for marketing of a drug under this section or section 262 of title 42, the Secretary shall establish panels of experts or use panels of experts established before November 21, 1997, or both.

(2) The Secretary may delegate the appointment and oversight authority granted under section 394 of this title to a director of a center or successor entity within the Food and Drug Administration.

(3) The Secretary shall make appointments to each panel established under paragraph (1) so that each panel shall consist of--

(A) members who are qualified by training and experience to evaluate the safety and effectiveness of the drugs to be referred to the panel and who, to the extent feasible, possess skill and experience in the development, manufacture, or utilization of such drugs;

(B) members with diverse expertise in such fields as clinical and administrative medicine, pharmacy, pharmacology, pharmacoconomics, biological and physical sciences, and other related professions;

(C) a representative of consumer interests, and a representative of interests of the drug manufacturing industry not directly affected by the matter to be brought before the panel; and

(D) two or more members who are specialists or have other expertise in the particular disease or condition for which the drug under review is proposed to be indicated.

Scientific, trade, and consumer organizations shall be afforded an

opportunity to nominate individuals for appointment to the panels. No individual who is in the regular full-time employ of the United States and engaged in the administration of this chapter may be a voting member of any panel. The Secretary shall designate one of the members of each panel to serve as chairman thereof.

(4) Each member of a panel shall publicly disclose all conflicts of interest that member may have with the work to be undertaken by the panel. No member of a panel may vote on any matter where the member or the immediate family of such member could gain financially from the advice given to the Secretary. The Secretary may grant a waiver of any conflict of interest requirement upon public disclosure of such conflict of interest if such waiver is necessary to afford the panel essential expertise, except that the Secretary may not grant a waiver for a member of a panel when the member's own scientific work is involved.

(5) The Secretary shall, as appropriate, provide education and training to each new panel member before such member participates in a panel's activities, including education regarding requirements under this chapter and related regulations of the Secretary, and the administrative processes and procedures related to panel meetings.

(6) Panel members (other than officers or employees of the United States), while attending meetings or conferences of a panel or otherwise engaged in its business, shall be entitled to receive compensation for each day so engaged, including traveltime, at rates to be fixed by the Secretary, but not to exceed the daily equivalent of the rate in effect for positions classified above grade GS-15 of the General Schedule. While serving away from their homes or regular places of business, panel members may be allowed travel expenses (including per diem in lieu of subsistence) as authorized by section 5703 of title 5, for persons in the Government service employed intermittently.

(7) The Secretary shall ensure that scientific advisory panels meet regularly and at appropriate intervals so that any matter to be reviewed by such a panel can be presented to the panel not more than 60 days after the matter is ready for such review. Meetings of the panel may be held using electronic communication to convene the meetings.

(8) Within 90 days after a scientific advisory panel makes recommendations on any matter under its review, the Food and Drug Administration official responsible for the matter shall review the conclusions and recommendations of the panel, and notify the affected persons of the final decision on the matter, or of the reasons that no such decision has been reached. Each such final decision shall be documented including the rationale for the decision.

(June 25, 1938, ch. 675, Sec. 505, 52 Stat. 1052; Pub. L. 86-507, Sec. 1(18), June 11, 1960, 74 Stat. 201; Pub. L. 87-781, title I, Secs. 102(b)-(d), 103(a), (b), 104(a)-(d)(2), Oct. 10, 1962, 76 Stat. 781-783, 784, 785; Pub. L. 92-387, Sec. 4(d), Aug. 16, 1972, 86 Stat. 562; Pub. L. 98-417, title I, Secs. 101, 102(a)-(b)(5), 103, 104, Sept. 24, 1984, 98 Stat. 1585, 1592, 1593, 1597; Pub. L. 102-282, Sec. 5, May 13, 1992, 106 Stat. 161; Pub. L. 103-80, Sec. 3(n), Aug. 13, 1993, 107 Stat. 777; Pub. L. 105-115, title I, Secs. 115, 117, 119, 120, 124(a), Nov. 21, 1997, 111 Stat. 2313, 2315, 2316, 2318, 2324; Pub. L. 106-113, div. B, Sec. 1000(a)(9) [title IV, Sec. 4732(b)(11)], Nov. 29, 1999, 113 Stat. 1536, 1501A-584; Pub. L. 107-109, Sec. 15(c)(1), Jan. 4, 2002, 115 Stat. 1420.)

References in Text

The General Schedule, referred to in subsec. (n)(6), is set out under section 5332 of Title 5, Government Organization and Employees.

Amendments

2002--Subsec. (i)(1)(D). Pub. L. 107-109 added subpar. (D).

1999--Subsec. (m). Pub. L. 106-113 substituted ``United States Patent and Trademark Office'' for ``Patent and Trademark Office of the Department of Commerce''.

1997--Subsec. (b)(1). Pub. L. 105-115, Sec. 115(b), inserted at end ``The Secretary shall, in consultation with the Director of the National Institutes of Health and with representatives of the drug manufacturing industry, review and develop guidance, as appropriate, on the inclusion of women and minorities in clinical trials required by clause (A).''

Subsec. (b)(4). Pub. L. 105-115, Sec. 119(a), added par. (4).

Subsec. (c)(4). Pub. L. 105-115, Sec. 124(a), added par. (4).

Subsec. (d). Pub. L. 105-115, Sec. 115(a), inserted at end ``If the Secretary determines, based on relevant science, that data from one adequate and well-controlled clinical investigation and confirmatory evidence (obtained prior to or after such investigation) are sufficient to establish effectiveness, the Secretary may consider such data and evidence to constitute substantial evidence for purposes of the preceding sentence.''

Subsec. (i). Pub. L. 105-115, Sec. 117, inserted ``(1)'' after ``(i)'', redesignated former pars. (1) to (3) as subpars. (A) to (C), respectively, of par. (1), added pars. (2) to (4), and struck out closing provisions which read as follows: ``Such regulations shall provide that such exemption shall be conditioned upon the manufacturer, or the sponsor of the investigation, requiring that experts using such drugs for investigational purposes certify to such manufacturer or sponsor that they will inform any human beings to whom such drugs, or any controls used in connection therewith, are being administered, or their representatives, that such drugs are being used for investigational purposes and will obtain the consent of such human beings or their representatives, except where they deem it not feasible or, in their professional judgment, contrary to the best interests of such human beings. Nothing in this subsection shall be construed to require any clinical investigator to submit directly to the Secretary reports on the investigational use of drugs.''

Subsec. (j)(2)(A)(i). Pub. L. 105-115, Sec. 119(b)(2)(A), substituted ``paragraph (7)'' for ``paragraph (6)''.

Subsec. (j)(3). Pub. L. 105-115, Sec. 119(b)(1)(B), added par. (3). Former par. (3) redesignated (4).

Subsec. (j)(4). Pub. L. 105-115, Sec. 119(b)(1)(A), (2)(B), redesignated par. (3) as (4) and in introductory provisions substituted ``paragraph (5)'' for ``paragraph (4)''.

Subsec. (j)(4)(I). Pub. L. 105-115, Sec. 119(b)(2)(C), substituted ``paragraph (6)'' for ``paragraph (5)''.

Subsec. (j)(5), (6). Pub. L. 105-115, Sec. 119(b)(1)(A), redesignated pars. (4) and (5) as (5) and (6), respectively. Former par. (6) redesignated (7).

Subsec. (j)(7). Pub. L. 105-115, Sec. 119(b)(1)(A), (2)(D), redesignated par. (6) as (7) and in subpar. (C) substituted ``paragraph (6)'' for ``paragraph (5)'' in two places. Former par. (7) redesignated (8).

Subsec. (j)(8), (9). Pub. L. 105-115, Sec. 119(b)(1)(A), redesignated pars. (7) and (8) as (8) and (9), respectively.

Subsec. (n). Pub. L. 105-115, Sec. 120, added subsec. (n).

1993--Subsec. (j)(6)(A)(ii). Pub. L. 103-80, Sec. 3(n)(1)(A), substituted ``Secretary'' for ``Secretrey''.

Subsec. (j)(6)(A)(iii). Pub. L. 103-80, Sec. 3(n)(1)(B), inserted

comma after ``published by the Secretary''.

Subsec. (k)(1). Pub. L. 103-80, Sec. 3(n)(2), substituted ``section. Regulations'' for ``section: Provided, however, That regulations''.

1992--Subsec. (j)(8). Pub. L. 102-282 added par. (8).

1984--Subsec. (a). Pub. L. 98-417, Sec. 102(b)(1), inserted ``or (j)'' after ``subsection (b)''.

Subsec. (b). Pub. L. 98-417, Secs. 102(a)(1), 103(a), designated existing provisions of subsec. (b) as par. (1) thereof and redesignated existing cls. (1) through (6) of such par. (1) as cls. (A) through (F) thereof, respectively, inserted requirement that the applicant file with the application the patent number and the expiration date of any patent which claims the drug for which the applicant submitted the application or which claims a method of using such drug and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner engaged in the manufacture, use, or sale of the drug, that the applicant amend the application to include such information if an application is filed under this subsection for a drug and a patent which claims such drug or a method of using such drug is issued after the filing date but before approval of the application, and that upon approval of the application, the Secretary publish the information submitted, and added pars. (2) and (3).

Subsec. (c). Pub. L. 98-417, Secs. 102(a)(2), (b)(2), 103(b), designated existing provisions of subsec. (c) as par. (1) thereof and in par. (1) as so designated substituted ``subsection (b) of this section'' for ``this subsection'' and redesignated former pars. (1) and (2) as subpars. (A) and (B), respectively, and added pars. (2) and (3).

Subsec. (d)(6), (7). Pub. L. 98-417, Sec. 102(a)(3)(A), added cl. (6) relating to the failure of the application to contain the patent information prescribed by subsec. (b) of this section, and redesignated former cl. (6) as (7).

Subsec. (e). Pub. L. 98-417, Sec. 102(a)(3)(B), in first sentence, added a new cl. (4) relating to the failure to file the patent information prescribed by subsec. (c) of this section within 30 days after the receipt of written notice from the Secretary specifying the failure to file such information, and redesignated former cl. (4) as (5).

Pub. L. 98-417, Sec. 102(b)(3), (4), in second sentence, inserted in provisions preceding cl. (1) ``submitted under subsection (b) or (j) of this section'' and in cl. (1) substituted ``under subsection (k) of this section or to comply with the notice requirements of section 360(k)(2) of this title'' for ``under subsection (j) of this section or to comply with the notice requirements of section 360(j)(2) of this title''.

Subsecs. (j), (k). Pub. L. 98-417, Sec. 101, added subsec. (j) and redesignated former subsec. (j) as (k).

Subsec. (k)(1). Pub. L. 98-417, Sec. 102(b)(5), substituted ``under subsection (b) or (j) of this section'' for ``pursuant to this section''.

Subsecs. (l), (m). Pub. L. 98-417, Sec. 104, added subsecs. (l) and (m).

1972--Subsec. (e). Pub. L. 92-387 inserted ``or to comply with the notice requirements of section 360(j)(2) of this title'' in cl. (1) of second sentence relating to the maintenance of records.

1962--Subsec. (a). Pub. L. 87-781, Sec. 104(a), inserted ``an approval of'' before ``an application''.

Subsec. (b). Pub. L. 87-781, Sec. 102(b), inserted ``and whether such drug is effective in use'' after ``is safe for use''.

Subsec. (c). Pub. L. 87-781, Sec. 104(b), substituted provisions requiring the Secretary, within 180 days after filing an application, or such additional period as the Secretary and the applicant agree upon, to either approve the application, if meeting the requirements of subsec.

(d) of this section, or give notice of opportunity for hearing on question of whether such application is approvable, and providing that if applicant requests hearing in writing within 30 days, the hearing shall begin within 90 days after expiration of said 30 days, unless the Secretary and applicant agree otherwise, that such hearing shall be expedited, and that the Secretary's order shall be issued within 90 days after date for filing final briefs, for provisions which had an application become effective on the sixtieth day after filing thereof unless prior thereto the Secretary postponed the date by written notice to such time, but not more than 180 days after filing, as the Secretary deemed necessary to study and investigate the application.

Subsec. (d). Pub. L. 87-781, Sec. 102(c), inserted references to subsec. (c), added cls. (5) and (6), provided that if after notice and opportunity for hearing, the Secretary finds that cls. (1) to (6) do not apply, he shall approve the application, and defined ``substantial evidence'' as used in this subsection and subsec. (e) of this section.

Subsec. (e). Pub. L. 87-781, Sec. 102(d), amended subsec. (e) generally, and among other changes, directed the Secretary to withdraw approval of an application if by tests, other scientific data or experience, or new evidence of clinical experience not contained in the application or available at the time of its approval, the drug is shown to be unsafe, or on the basis of new information, there is shown a lack of substantial evidence that the drug has the effect it is represented to have, and provided that if the Secretary, or acting Secretary, finds there is an imminent hazard to the public health, he may suspend approval immediately, notify the applicant, and give him opportunity for an expedited hearing, that the Secretary may withdraw approval if the applicant fails to establish a system for maintaining required records, or has repeatedly or deliberately failed to maintain records and make reports, or has refused access to, or copying or verification of such records, or if the Secretary finds on new evidence that the methods, facilities and controls in the manufacturing, processing, and packing are inadequate to assure and preserve the drugs' identity, strength, quality and purity, and were not made adequate within a reasonable time after receipt of written notice thereof, or finds on new evidence, that the labeling is false or misleading and was not corrected within a reasonable time after receipt of written notice thereof.

Subsec. (f). Pub. L. 87-781, Sec. 104(c), substituted provisions requiring the Secretary to revoke any previous order under subsecs. (d) or (e) of this section refusing, withdrawing, or suspending approval of an application and to approve such application or reinstate such approval, for provisions which required him to revoke an order refusing effectiveness to an application.

Subsec. (h). Pub. L. 87-781, Sec. 104(d)(1), (2), inserted ``as provided in section 2112 of title 28'', and ``except that until the filing of the record the Secretary may modify or set aside his order'', substituted ``or withdrawing approval of an application under this section'' for ``to permit the application to become effective, or suspending the effectiveness of the application'', ``United States court of appeals for the circuit'' for ``district court of the United States within any district'', ``Court of Appeals for the District of Columbia Circuit'' for ``District Court for the District of Columbia'', ``transmitted by the clerk of the court to'' for ``served upon'', and ``by the Supreme Court of the United States upon certiorari or certification as provided in section 1254 of title 28'' for ``as provided in sections 225, 346, and 347 of title 28, as amended, and in section 7, as amended, of the Act entitled `An Act to establish a Court of Appeals for the District of Columbia', approved February 9, 1893'', and eliminated ``upon'' before ``any officer designated'', ``a transcript of'' before ``the record'' and ``and decree'' before ``of the

court affirming''.

Subsec. (i). Pub. L. 87-781, Sec. 103(b), inserted ``the foregoing subsections of'' after ``operation of'', and ``and effectiveness'' after ``safety'', and provided that the regulations may condition exemptions upon the submission of reports of preclinical tests to justify the proposed clinical testing, upon the obtaining by the manufacturer or sponsor of the investigation of a new drug of a signed agreement from each of the investigators that patients to whom the drug is administered will be under his supervision or under investigators responsible to him, and that he will not supply such drug to any other investigator, or to clinics, for administration to human beings, or upon the establishment and maintenance of records and reports of data obtained by the investigational use of such drug, as the Secretary finds will enable him to evaluate the safety and effectiveness of such drug, and provided that the regulations shall condition an exemption upon the manufacturer or sponsor of the investigation requiring that experts using such drugs certify that they will inform humans to whom such drugs or any controls connected therewith are administered, or their representatives, and will obtain the consent of such people where feasible and not contrary to the best interests of such people, and that reports on the investigational use of drugs are not required to be submitted directly to the Secretary.

Subsec. (j). Pub. L. 87-781, Sec. 103(a), added subsec. (j).

1960--Subsec. (g). Pub. L. 86-507 inserted ``or by certified mail'' after ``registered mail''.

Effective Date of 1999 Amendment

Amendment by Pub. L. 106-113 effective 4 months after Nov. 29, 1999, see section 1000(a)(9) [title IV, Sec. 4731] of Pub. L. 106-113, set out as a note under section 1 of Title 35, Patents.

Effective Date of 1997 Amendment

Amendment by Pub. L. 105-115 effective 90 days after Nov. 21, 1997, except as otherwise provided, see section 501 of Pub. L. 105-115, set out as a note under section 321 of this title.

Effective Date of 1984 Amendment

Section 105 of Pub. L. 98-417 provided that:

``(a) The Secretary of Health and Human Services shall promulgate, in accordance with the notice and comment requirements of section 553 of title 5, United States Code, such regulations as may be necessary for the administration of section 505 of the Federal Food, Drug, and Cosmetic Act [this section], as amended by sections 101, 102, and 103 of this Act, within one year of the date of enactment of this Act [Sept. 24, 1984].

``(b) During the period beginning sixty days after the date of the enactment of this Act [Sept. 24, 1984], and ending on the date regulations promulgated under subsection (a) take effect, abbreviated new drug applications may be submitted in accordance with the provisions of section 314.2 of title 21 of the Code of Federal Regulations and shall be considered as suitable for any drug which has been approved for safety and effectiveness under section 505(c) of the Federal Food, Drug, and Cosmetic Act [subsec. (c) of this section] before the date of the enactment of this Act. If any such provision is inconsistent with the requirements of section 505(j) of the Federal Food, Drug, and Cosmetic

Act, the Secretary shall consider the application under the applicable requirements of such section. The Secretary of Health and Human Services may not approve such an abbreviated new drug application which is filed for a drug which is described in sections 505(c)(3)(D) and 505(j)(4)(D) of the Federal Food, Drug, and Cosmetic Act, except in accordance with such section.''

Effective Date of 1972 Amendment

Amendment by Pub. L. 92-387 effective on first day of sixth month beginning after Aug. 16, 1972, see section 5 of Pub. L. 92-387, set out as a note under section 360 of this title.

Effective Date of 1962 Amendment

Amendment by Pub. L. 87-781 effective on first day of seventh calendar month following October 1962, see section 107 of Pub. L. 87-781, set out as a note under section 321 of this title.

Construction of Amendments by Pub. L. 102-282

Amendment by Pub. L. 102-282 not to preclude any other civil, criminal, or administrative remedy provided under Federal or State law, including any private right of action against any person for the same action subject to any action or civil penalty under an amendment made by Pub. L. 102-282, see section 7 of Pub. L. 102-282, set out as a note under section 335a of this title.

Transfer of Functions

For transfer of functions of Federal Security Administrator to Secretary of Health, Education, and Welfare [now Health and Human Services], and of Food and Drug Administration in the Department of Agriculture to Federal Security Agency, see note set out under section 41 of this title.

Report on Patient Access to New Therapeutic Agents for Pediatric Cancer

Pub. L. 107-109, Sec. 15(d), Jan. 4, 2002, 115 Stat. 1421, provided that: ``Not later than January 31, 2003, the Secretary of Health and Human Services, acting through the Commissioner of Food and Drugs and in consultation with the Director of the National Institutes of Health, shall submit to the Committee on Health, Education, Labor, and Pensions of the Senate and the Committee on Energy and Commerce of the House of Representatives a report on patient access to new therapeutic agents for pediatric cancer, including access to single patient use of new therapeutic agents.''

Data Requirements for Drugs and Biologics

Section 118 of Pub. L. 105-115 provided that: ``Within 12 months after the date of enactment of this Act [Nov. 21, 1997], the Secretary of Health and Human Services, acting through the Commissioner of Food and Drugs, shall issue guidance that describes when abbreviated study reports may be submitted, in lieu of full reports, with a new drug

application under section 505(b) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(b)) and with a biologics license application under section 351 of the Public Health Service Act (42 U.S.C. 262) for certain types of studies. Such guidance shall describe the kinds of studies for which abbreviated reports are appropriate and the appropriate abbreviated report formats.''

Requirements for Review of Approval Procedures and Current Good Manufacturing Practices for Positron Emission Technology

Section 121(c) of Pub. L. 105-115 provided that:

``(1) Procedures and requirements.--

``(A) In general.--In order to take account of the special characteristics of positron emission tomography drugs and the special techniques and processes required to produce these drugs, not later than 2 years after the date of enactment of this Act [Nov. 21, 1997], the Secretary of Health and Human Services shall establish--

``(i) appropriate procedures for the approval of positron emission tomography drugs pursuant to section 505 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355); and

``(ii) appropriate current good manufacturing practice requirements for such drugs.

``(B) Considerations and consultation.--In establishing the procedures and requirements required by subparagraph (A), the Secretary of Health and Human Services shall take due account of any relevant differences between not-for-profit institutions that compound the drugs for their patients and commercial manufacturers of the drugs. Prior to establishing the procedures and requirements, the Secretary of Health and Human Services shall consult with patient advocacy groups, professional associations, manufacturers, and physicians and scientists licensed to make or use positron emission tomography drugs.

``(2) Submission of new drug applications and abbreviated new drug applications.--

``(A) In general.--Except as provided in subparagraph (B), the Secretary of Health and Human Services shall not require the submission of new drug applications or abbreviated new drug applications under subsection (b) or (j) of section 505 (21 U.S.C. 355), for compounded positron emission tomography drugs that are not adulterated drugs described in section 501(a)(2)(C) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 351(a)(2)(C)) (as amended by subsection (b)), for a period of 4 years after the date of enactment of this Act [Nov. 21, 1997], or for 2 years after the date on which the Secretary establishes procedures and requirements under paragraph (1), whichever is longer.

``(B) Exception.--Nothing in this Act [see Short Title of 1997 Amendment note set out under section 301 of this title] shall prohibit the voluntary submission of such applications or the review of such applications by the Secretary of Health and Human Services. Nothing in this Act shall constitute an exemption for a positron emission tomography drug from the requirements of regulations issued under section 505(i) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(i)).''

``Compounded Positron Emission Topography Drug'' Defined

Section 121(e) of Pub. L. 105-115 provided that: ``As used in this

section [amending sections 321 and 351 of this title and enacting provisions set out as notes under this section and section 351 of this title], the term `compounded positron emission tomography drug' has the meaning given the term in section 201 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321).'

Requirements for Radiopharmaceuticals

Section 122 of Pub. L. 105-115 provided that:

``(a) Requirements.--

``(1) Regulations.--

``(A) Proposed regulations.--Not later than 180 days after the date of enactment of this Act [Nov. 21, 1997], the Secretary of Health and Human Services, after consultation with patient advocacy groups, associations, physicians licensed to use radiopharmaceuticals, and the regulated industry, shall issue proposed regulations governing the approval of radiopharmaceuticals. The regulations shall provide that the determination of the safety and effectiveness of such a radiopharmaceutical under section 505 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355) or section 351 of the Public Health Service Act (42 U.S.C. 262) shall include consideration of the proposed use of the radiopharmaceutical in the practice of medicine, the pharmacological and toxicological activity of the radiopharmaceutical (including any carrier or ligand component of the radiopharmaceutical), and the estimated absorbed radiation dose of the radiopharmaceutical.

``(B) Final regulations.--Not later than 18 months after the date of enactment of this Act, the Secretary shall promulgate final regulations governing the approval of the radiopharmaceuticals.

``(2) Special rule.--In the case of a radiopharmaceutical, the indications for which such radiopharmaceutical is approved for marketing may, in appropriate cases, refer to manifestations of disease (such as biochemical, physiological, anatomic, or pathological processes) common to, or present in, one or more disease states.

``(b) Definition.--In this section, the term `radiopharmaceutical' means--

``(1) an article--

``(A) that is intended for use in the diagnosis or monitoring of a disease or a manifestation of a disease in humans; and

``(B) that exhibits spontaneous disintegration of unstable nuclei with the emission of nuclear particles or photons; or

``(2) any nonradioactive reagent kit or nuclide generator that is intended to be used in the preparation of any such article.'

Special Rule

Section 123(f) of Pub. L. 105-115 provided that: ``The Secretary of Health and Human Services shall take measures to minimize differences in the review and approval of products required to have approved biologics license applications under section 351 of the Public Health Service Act (42 U.S.C. 262) and products required to have approved new drug applications under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(b)(1)).'

Transition

Section 125(d) of Pub. L. 105-115 provided that:

``(1) In general.--An application that was approved by the Secretary of Health and Human Services before the date of the enactment of this Act [Nov. 21, 1997] for the marketing of an antibiotic drug under section 507 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 357), as in effect on the day before the date of the enactment of this Act, shall, on and after such date of enactment, be considered to be an application that was submitted and filed under section 505(b) of such Act (21 U.S.C. 355(b)) and approved for safety and effectiveness under section 505(c) of such Act (21 U.S.C. 355(c)), except that if such application for marketing was in the form of an abbreviated application, the application shall be considered to have been filed and approved under section 505(j) of such Act (21 U.S.C. 355(j)).

``(2) Exception.--The following subsections of section 505 (21 U.S.C. 355) shall not apply to any application for marketing in which the drug that is the subject of the application contains an antibiotic drug and the antibiotic drug was the subject of any application for marketing received by the Secretary of Health and Human Services under section 507 of such Act (21 U.S.C. 357) before the date of the enactment of this Act [Nov. 21, 1997]:

``(A) (i) Subsections (c) (2), (d) (6), (e) (4), (j) (2) (A) (vii), (j) (2) (A) (viii), (j) (2) (B), (j) (4) (B), and (j) (4) (D); and

``(ii) The third and fourth sentences of subsection (b) (1) (regarding the filing and publication of patent information); and

``(B) Subsections (b) (2) (A), (b) (2) (B), (b) (3), and (c) (3) if the investigations 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.

``(3) Publication.--For purposes of this section, the Secretary is authorized to make available to the public the established name of each antibiotic drug that was the subject of any application for marketing received by the Secretary for Health and Human Services under section 507 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 357) before the date of enactment of this Act [Nov. 21, 1997].''

Termination of Advisory Panels

Advisory panels established after Jan. 5, 1973, to terminate not later than the expiration of the 2-year period beginning on the date of their establishment, unless, in the case of a panel established by the President or an officer of the Federal Government, such panel is renewed by appropriate action prior to the expiration of such 2-year period, or in the case of a panel established by Congress, its duration is otherwise provided for by law. See sections 3(2) and 14 of Pub. L. 92-463, Oct. 6, 1972, 86 Stat. 770, 776, set out in the Appendix to Title 5, Government Organization and Employees.

Appeals Taken Prior to October 10, 1962

Section 104(d) (3) of Pub. L. 87-781 made amendments to subsec. (h) of this section inapplicable to any appeal taken prior to Oct. 10, 1962.

Section Referred to in Other Sections

This section is referred to in sections 321, 331, 333, 334, 335a, 352, 353, 353a, 355a, 355b, 356, 356a, 356c, 360, 360b, 360j, 360aa to 360ee, 360aaa, 360bbb, 360bbb-1, 374, 379g, 379h, 379r, 381, 382, 384, 802, 811, 827 of this title; title 10 section 1107; title 26 section 45C; title 28 section 2201; title 35 sections 155A, 156, 271; title 42 sections 236, 262, 282, 284m, 300cc-12, 300cc-13, 300cc-17, 1395y, 1396r-8.

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(e) Quantitative or semiquantitative formulas.

(f) Information on product design or construction.

(ii) Material submitted under paragraph (j)(2) of this section is to be segregated from all other submitted material and clearly so marked. A person who does not agree that a submission is properly subject to paragraph (j)(2) may request a ruling from the Associate Commissioner for Public Affairs whose decision is final, subject to judicial review under § 20.48.

(3) Material listed in paragraph (j)(2)(i) (a) and (b) of this section may be disclosed under a protective order issued by the administrative law judge or other presiding officer at a hearing referenced in paragraph (j)(2)(i). The administrative law judge or presiding officer shall permit disclosure of the data only in camera and only to the extent necessary for the proper conduct of the hearing. The administrative law judge or presiding officer shall direct to whom the information is to be made available (e.g., to parties or participants, or only to counsel for parties or participants), and persons not specifically permitted access to the data will be excluded from the in camera part of the proceeding. The administrative law judge or other presiding officer may impose other conditions or safeguards. The limited availability of material under this paragraph does not constitute prior disclosure to the public as defined in § 20.81, and no information subject to a particular order is to be submitted to or received or considered by FDA in support of a petition or other request from any other person.

[44 FR 22323, Apr. 13, 1979, as amended at 46 FR 8455, Jan. 27, 1981; 49 FR 7363, Feb. 29, 1984; 54 FR 9034, Mar. 3, 1989; 59 FR 14363, Mar. 28, 1994; 64 FR 69190, Dec. 10, 1999; 65 FR 56477, Sept. 19, 2000; 66 FR 56035, Nov. 6, 2001; 66 FR 66742, Dec. 27, 2001; 68 FR 25285, May 12, 2003]

§ 10.25 Initiation of administrative proceedings.

An administrative proceeding may be initiated in the following three ways:

(a) An interested person may petition the Commissioner to issue, amend, or revoke a regulation or order, or to take or refrain from taking any other form

of administrative action. A petition must be either: (1) In the form specified in other applicable FDA regulations, e.g., the form for a color additive petition in § 71.1, for a food additive petition in § 171.1, for a new drug application in § 314.50, for a new animal drug application in § 514.1, or (2) in the form for a citizen petition in § 10.30.

(b) The Commissioner may initiate a proceeding to issue, amend, or revoke a regulation or order or take or refrain from taking any other form of administrative action. FDA has primary jurisdiction to make the initial determination on issues within its statutory mandate, and will request a court to dismiss, or to hold in abeyance its determination of or refer to the agency for administrative determination, any issue which has not previously been determined by the agency or which, if it has previously been determined, the agency concluded should be reconsidered and subject to a new administrative determination. The Commissioner may utilize any of the procedures established in this part in reviewing and making a determination on any matter initiated under this paragraph.

(c) The Commissioner will institute a proceeding to determine whether to issue, amend, or revoke a regulation or order, or take or refrain from taking any other form of administrative action whenever any court, on its own initiative, holds in abeyance or refers any matter to the agency for an administrative determination and the Commissioner concludes that an administrative determination is feasible within agency priorities and resources.

[44 FR 22323, Apr. 13, 1979, as amended at 54 FR 9034, Mar. 3, 1989]

§ 10.30 Citizen petition.

(a) This section applies to any petition submitted by a person (including a person who is not a citizen of the United States) except to the extent that other sections of this chapter apply different requirements to a particular matter.

(b) A petition (including any attachments) must be submitted in accordance with § 10.20 and in the following form:

(Date) _____

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Division of Dockets Management, Food and Drug Administration, Department of Health and Human Services, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

CITIZEN PETITION

The undersigned submits this petition under _____ (relevant statutory sections, if known) of the _____ (Federal Food, Drug, and Cosmetic Act or the Public Health Service Act or any other statutory provision for which authority has been delegated to the Commissioner of Food and Drugs under 21 CFR 5.10) to request the Commissioner of Food and Drugs to _____ (issue, amend, or revoke a regulation or order or take or refrain from taking any other form of administrative action).

A. Action requested

(1) If the petition requests the Commissioner to issue, amend, or revoke a regulation, the exact wording of the existing regulation (if any) and the proposed regulation or amendment requested.)

(2) If the petition requests the Commissioner to issue, amend, or revoke an order, a copy of the exact wording of the citation to the existing order (if any) and the exact wording requested for the proposed order.)

(3) If the petition requests the Commissioner to take or refrain from taking any other form of administrative action, the specific action or relief requested.)

B. Statement of grounds

(A full statement, in a well organized format, of the factual and legal grounds on which the petitioner relies, including all relevant information and views on which the petitioner relies, as well as representative information known to the petitioner which is unfavorable to the petitioner's position.)

C. Environmental impact

(A) Claim for categorical exclusion under §§ 25.30, 25.31, 25.32, 25.33, or §25.34 of this chapter or an environmental assessment under § 25.40 of this chapter.)

D. Economic impact

(The following information is to be submitted only when requested by the Commissioner following review of the petition: A statement of the effect of requested action on: (1) Cost (and price) increases to industry, government, and consumers; (2) productivity of wage earners, businesses, or government; (3) competition; (4) supplies of important materials, products, or services; (5) employment; and (6) energy supply or demand.)

E. Certification

The undersigned certifies, that, to the best knowledge and belief of the undersigned, this

petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner which are unfavorable to the petition.

(Signature) _____
(Name of petitioner) _____
(Mailing address) _____
(Telephone number) _____

(c) A petition which appears to meet the requirements of paragraph (b) of this section and §10.20 will be filed by the Division of Dockets Management, stamped with the date of filing, and assigned a docket number. The docket number identifies the file established by the Division of Dockets Management for all submissions relating to the petition, as provided in this part. Subsequent submissions relating to the matter must refer to the docket number and will be filed in the docket file. Related petitions may be filed together and given the same docket number. The Division of Dockets Management will promptly notify the petitioner in writing of the filing and docket number of a petition.

(d) An interested person may submit written comments to the Division of Dockets Management on a filed petition, which comments become part of the docket file. The comments are to specify the docket number of the petition and may support or oppose the petition in whole or in part. A request for alternative or different administrative action must be submitted as a separate petition.

(e)(1) The Commissioner shall, in accordance with paragraph (e)(2), rule upon each petition filed under paragraph (c) of this section, taking into consideration (i) available agency resources for the category of subject matter, (ii) the priority assigned to the petition considering both the category of subject matter involved and the overall work of the agency, and (iii) time requirements established by statute.

(2) Except as provided in paragraph (e)(4) of this section, the Commissioner shall furnish a response to each petitioner within 180 days of receipt of the petition. The response will either:

(i) Approve the petition, in which case the Commissioner shall concurrently take appropriate action (e.g.,

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publication of a FEDERAL REGISTER notice implementing the approval;

(ii) Deny the petition; or

(iii) Provide a tentative response, indicating why the agency has been unable to reach a decision on the petition, e.g., because of the existence of other agency priorities, or a need for additional information. The tentative response may also indicate the likely ultimate agency response, and may specify when a final response may be furnished.

(3) The Commissioner may grant or deny such a petition, in whole or in part, and may grant such other relief or take other action as the petition warrants. The petitioner is to be notified in writing of the Commissioner's decision. The decision will be placed in the public docket file in the office of the Division of Dockets Management and may also be in the form of a notice published in the FEDERAL REGISTER.

(4) The Commissioner shall furnish a response to each petitioner within 90 days of receipt of a petition filed under section 505(j)(2)(C) of the act. The response will either approve or disapprove the petition. Agency action on a petition shall be governed by § 314.93 of this chapter.

(f) If a petition filed under paragraph (c) of this section requests the Commissioner to issue, amend, or revoke a regulation, § 10.40 or § 10.50 also apply.

(g) A petitioner may supplement, amend, or withdraw a petition in writing without agency approval and without prejudice to resubmission at any time until the Commissioner rules on the petition, unless the petition has been referred for a hearing under parts 12, 13, 14, or 15. After a ruling or referral, a petition may be supplemented, amended, or withdrawn only with the approval of the Commissioner. The Commissioner may approve withdrawal, with or without prejudice against resubmission of the petition.

(h) In reviewing a petition the Commissioner may use the following procedures:

(1) Conferences, meetings, discussions, and correspondence under § 10.65.

(2) A hearing under parts 12, 13, 14, 15, or 16.

(3) A FEDERAL REGISTER notice requesting information and views.

(4) A proposal to issue, amend, or revoke a regulation, in accordance with § 10.40 or § 12.20.

(5) Any other specific public procedure established in this chapter and expressly applicable to the matter.

(i) The record of the administrative proceeding consists of the following:

(1) The petition, including all information on which it relies, filed by the Division of Dockets Management.

(2) All comments received on the petition, including all information submitted as a part of the comments.

(3) If the petition resulted in a proposal to issue, amend, or revoke a regulation, all of the documents specified in § 10.40(g).

(4) The record, consisting of any transcripts, minutes of meetings, reports, FEDERAL REGISTER notices, and other documents resulting from the optional procedures specified in paragraph (h) of this section, except a transcript of a closed portion of a public advisory committee meeting.

(5) The Commissioner's decision on the petition, including all information identified or filed by the Commissioner with the Division of Dockets Management as part of the record supporting the decision.

(6) All documents filed with the Division of Dockets Management under § 10.65(h).

(7) If a petition for reconsideration or for a stay of action is filed under paragraph (j) of this section, the administrative record specified in § 10.33(k) or § 10.35(h).

(j) The administrative record specified in paragraph (i) of this section is the exclusive record for the Commissioner's decision. The record of the administrative proceeding closes on the date of the Commissioner's decision unless some other date is specified. Thereafter any interested person may submit a petition for reconsideration under § 10.33 or a petition for stay of action under § 10.35. A person who wishes to rely upon information or views not included in the administrative record shall submit them to the Commissioner with a new petition to modify the decision in accordance with this section.

(k) This section does not apply to the referral of a matter to a United States

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attorney for the initiation of court enforcement action and related correspondence, or to requests, suggestions, and recommendations made informally in routine correspondence received by FDA. Routine correspondence does not constitute a petition within the meaning of this section unless it purports to meet the requirements of this section. Action on routine correspondence does not constitute final administrative action subject to judicial review under § 10.45.

(1) The Division of Dockets Management will maintain a chronological list of each petition filed under this section and § 10.85, but not of petitions submitted elsewhere in the agency under § 10.25(a)(1), showing:

- (1) The docket number;
- (2) The date the petition was filed by the Division of Dockets Management;
- (3) The name of the petitioner;
- (4) The subject matter involved; and
- (5) The disposition of the petition.

[44 FR 22323, Apr. 13, 1979, as amended at 46 FR 8455, Jan. 27, 1981; 50 16656, Apr. 26, 1985; 54 FR 9034, Mar. 3, 1989; 57 FR 17980, Apr. 28, 1992; 59 FR 14364, Mar. 28, 1994; 62 FR 40592, July 29, 1997; 66 FR 6467, Jan. 22, 2001; 66 FR 12848, Mar. 1, 2001]

§ 10.33 Administrative reconsideration of action.

(a) The Commissioner may at any time reconsider a matter, on the Commissioner's own initiative or on the petition of an interested person.

(b) An interested person may request reconsideration of part or all of a decision of the Commissioner on a petition submitted under § 10.25. Each request for reconsideration must be submitted in accordance with § 10.20 and in the following form no later than 30 days after the date of the decision involved. The Commissioner may, for good cause, permit a petition to be filed after 30 days. In the case of a decision published in the FEDERAL REGISTER, the day of publication is the day of decision.

(Date) _____

Division of Dockets Management, Food and Drug Administration, Department of Health and Human Services, rm. 1-23, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

PETITION FOR RECONSIDERATION

[Docket No.]

The undersigned submits this petition for reconsideration of the decision of the Commissioner of Food and Drugs in Docket No. _____.

A. Decision involved

(A concise statement of the decision of the Commissioner which the petitioner wishes to have reconsidered.)

B. Action requested

(The decision which the petitioner requests the Commissioner to make upon reconsideration of the matter.)

C. Statement of grounds

(A full statement, in a well-organized format, of the factual and legal grounds upon which the petitioner relies. The grounds must demonstrate that relevant information and views contained in the administrative record were not previously or not adequately considered by the Commissioner.

(No new information or views may be included in a petition for reconsideration.)

(Signature) _____
(Name of petitioner) _____
(Mailing address) _____
(Telephone number) _____

(c) A petition for reconsideration relating to a petition submitted under § 10.25(a)(2) is subject to the requirements of § 10.30 (c) and (d), except that it is filed in the same docket file as the petition to which it relates.

(d) The Commissioner shall promptly review a petition for reconsideration. The Commissioner may grant the petition when the Commissioner determines it is in the public interest and in the interest of justice. The Commissioner shall grant a petition for reconsideration in any proceeding if the Commissioner determines all of the following apply:

- (1) The petition demonstrates that relevant information or views contained in the administrative record were not previously or not adequately considered.
- (2) The petitioner's position is not frivolous and is being pursued in good faith.
- (3) The petitioner has demonstrated sound public policy grounds supporting reconsideration.
- (4) Reconsideration is not outweighed by public health or other public interests.

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.

(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.

§314.94 Content and format of an abbreviated application.

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

(a) *Abbreviated new drug applications.* 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 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 abbreviated new drug application submission.* An abbreviated new drug application must refer to a listed drug. Ordinarily, that listed drug will be the drug product selected by the agency as the reference standard for conducting bioequivalence testing. The application shall contain:

(i) The name of the reference listed drug, including its dosage form and strength. For an abbreviated new drug application based on an approved 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)(4)(D) of the act.

(iii) For an abbreviated new drug application based on an approved petition under § 10.30 of this chapter or § 314.93, a reference to 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; or

(ii) If the abbreviated new drug application is submitted under a petition approved under § 314.93, the results of any bioavailability or bioequivalence testing required by the agency, or any other information required by the 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 con-

taining 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 bioequivalence study contained in the abbreviated new drug application, 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 of this chapter, or was not subject to the regulations under § 56.104 or § 56.105 of this chapter and that each study 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)(4)(D) of the act.

(9) *Chemistry, manufacturing, and controls.* (i) The information required under § 314.50(d)(1), 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) *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, drug product, or method of use.* (A) 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 and for which information is required to be filed under section 505(b) and (c) of the act and § 314.53. For each such patent, the applicant shall 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) 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 is submitted. The applicant shall 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.

The certification shall 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 representatives and to the holder of the approved application for the listed drug, and with the requirements under § 314.95(c) with respect to the content of the notice.

(B) If the 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, the appropriate patent certification under paragraph (a)(12)(i) 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 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 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 any indications that are covered by the use patent, a statement explaining that the method of use patent does not claim any of the proposed indications.

(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 and § 314.53 or in the opinion of the applicant, is claimed by a 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 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") as to that patent and a statement that it has been granted a patent license.

(vi) *Late submission of patent information.* If a patent on the listed drug is issued and the holder of the approved application for the listed drug does not submit the required information on the patent within 30 days of issuance of the patent, an applicant who submitted an abbreviated new drug application for that drug that contained an appropriate patent certification before the submission of the patent information is

not required to submit an amended certification. 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.

(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 submit an appropriate certification for each relevant patent.

(viii) *Amended certifications.* A certification 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. 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 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 submit an amended certification by letter or as an amendment to a pending application or by letter to an approved application. Once an amendment or letter is submitted, the application will no longer be considered to contain the prior certification.

(A) *After finding of infringement.* An applicant who has submitted a certification under paragraph (a)(12)(i)(A)(4) of this section and is sued for patent infringement within 45 days of the re-

ceipt of notice sent under § 314.95 shall amend the certification if a final judgment in the action against the applicant is entered finding the patent to be infringed. In the amended certification, the applicant shall certify under paragraph (a)(12)(i)(A)(3) of this section that the patent will expire on a specific date. Once an amendment or letter for the change has been submitted, the application will no longer be considered to be one containing a certification under paragraph (a)(12)(i)(A)(4) of this section. If a final judgment finds the patent to be invalid and infringed, an amended certification is not required.

(B) *After removal of a patent from the list.* If a patent is removed from the list, any applicant with a pending application (including a tentatively approved application with a delayed effective date) who has made a certification with respect to such patent shall amend 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 state the reason for the change in certification (that the patent is or has been removed from the list). 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 or letter for the change has been submitted, the application will no longer be considered to be one containing a certification under paragraph (a)(12)(i)(A)(4) of this section.

(C) *Other amendments.* (1) Except as provided in paragraphs (a)(12)(vi) and (a)(12)(viii)(C)(2) of this section, an applicant shall amend a submitted certification if, at any time before the effective date of the approval of the application, the applicant learns that the submitted certification is no longer accurate.

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

(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.* (1) The applicant shall submit a complete archival copy of the abbreviated application as required under paragraphs (a) and (c) 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 all or portions of the archival copy of the abbreviated application in any form (e.g., microfiche, optical disc, and magnetic tape) that the applicant and FDA agree is acceptable.

(2) For abbreviated new drug applications, the applicant shall submit a review copy of the abbreviated application that contains two separate sections. One section shall contain the information described under paragraphs (a)(2) through (a)(6), (a)(8), and (a)(9) of this section 505(j)(2)(A)(vii) of the act and one copy of the analytical methods 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 methods. The other section shall 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).

(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.

[57 FR 17983, Apr. 28, 1992; 57 FR 29353, July 1, 1992, as amended at 58 FR 47352, Sept. 8, 1993; 59 FR 50364, Oct. 3, 1994; 63 FR 5252, Feb. 2, 1998; 63 FR 66399, Dec. 1, 1998; 64 FR 401, Jan. 5, 1999; 65 FR 56479, Sept. 19, 2000; 67 FR 77672, Dec. 19, 2002]

EFFECTIVE DATE NOTE: At 68 FR 69019, Dec. 11, 2003, §314.94 was amended by revising paragraph (d)(1), effective June 8, 2004. For the convenience of the user, the revised text is set forth as follows:

§314.94 Content and format of an abbreviated application.

* * * * *

(d) * * * (1) The applicant must submit a complete archival copy of the abbreviated application as required under paragraphs (a) and (c) 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.

(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

§ 314.95

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).

* * * * *

§ 314.95 Notice of certification of invalidity 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 that the applicant certifies under § 314.94(a)(12) is invalid, unenforceable, or will not be infringed, the applicant shall send notice of such certification by registered or certified mail, return receipt requested to each of the following persons:

(1) Each owner of the patent which 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 under section 505(b) of the act for the listed drug that is claimed by the patent and for which the applicant is seeking approval, or, if the application holder does not reside or maintain a place of business within the United States, the application holder's attorney, agent, or other authorized official. The name and address of the application holder or its attorney, agent, or authorized official may be obtained from the Division of Drug Information Resources (HFD-80), Center for Drug Evaluation and Research, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857.

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

(b) *Sending the notice.* The applicant shall send the notice required by paragraph (a) of this section when it receives from FDA an acknowledgment letter stating that its abbreviated new drug application is sufficiently complete to permit a substantive review. 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.

(c) *Contents of a notice.* In the notice, the applicant shall cite section 505(j)(2)(B)(ii) of the act and shall include, but not be limited to, the following information:

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

(2) The abbreviated application number.

(3) The established name, if any, as defined in section 502(e)(3) of the 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 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 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 does not reside or have a place of business in the United States, the name and address of an

From the U.S. Code Online via GPO Access
[wais.access.gpo.gov]
[Laws in effect as of January 7, 2003]
[Document not affected by Public Laws enacted between
January 7, 2003 and February 12, 2003]
[CITE: 21USC355a]

TITLE 21--FOOD AND DRUGS

CHAPTER 9--FEDERAL FOOD, DRUG, AND COSMETIC ACT

SUBCHAPTER V--DRUGS AND DEVICES

Part A--Drugs and Devices

Sec. 355a. Pediatric studies of drugs

(a) Definitions

As used in this section, the term ``pediatric studies'' or ``studies'' means at least one clinical investigation (that, at the Secretary's discretion, may include pharmacokinetic studies) in pediatric age groups (including neonates in appropriate cases) in which a drug is anticipated to be used.

(b) Market exclusivity for new drugs

If, prior to approval of an application that is submitted under section 355(b)(1) of this title, the Secretary determines that information relating to the use of a new drug in the pediatric population may produce health benefits in that population, the Secretary makes a written request for pediatric studies (which shall include a timeframe for completing such studies), and such studies are completed within any such timeframe and the reports thereof submitted in accordance with subsection (d)(2) of this section or accepted in accordance with subsection (d)(3) of this section--

(1) (A) (i) the period referred to in subsection (c)(3)(D)(ii) of section 355 of this title, and in subsection (j)(5)(D)(ii) of such section, is deemed to be five years and six months rather than five years, and the references in subsections (c)(3)(D)(ii) and (j)(5)(D)(ii) of such section to four years, to forty-eight months, and to seven and one-half years are deemed to be four and one-half years, fifty-four months, and eight years, respectively; or

(ii) the period referred to in clauses (iii) and (iv) of subsection (c)(3)(D) of such section, and in clauses (iii) and (iv) of subsection (j)(5)(D) of such section, is deemed to be three years and six months rather than three years; and

(B) if the drug is designated under section 360bb of this title for a rare disease or condition, the period referred to in section 360cc(a) of this title is deemed to be seven years and six months rather than seven years; and

(2) (A) if the drug is the subject of--

(i) a listed patent for which a certification has been submitted under subsection (b)(2)(A)(ii) or (j)(2)(A)(vii)(II) of section 355 of this title and for which pediatric studies were submitted prior to the expiration of the patent (including any patent extensions); or

(ii) a listed patent for which a certification has been

submitted under subsections (b) (2) (A) (iii) or (j) (2) (A) (vii) (III) of section 355 of this title,

the period during which an application may not be approved under section 355(c) (3) of this title or section 355(j) (4) (B) of this title shall be extended by a period of six months after the date the patent expires (including any patent extensions); or

(B) if the drug is the subject of a listed patent for which a certification has been submitted under subsection (b) (2) (A) (iv) or (j) (2) (A) (vii) (IV) of section 355 of this title, and in the patent infringement litigation resulting from the certification the court determines that the patent is valid and would be infringed, the period during which an application may not be approved under section 355(c) (3) of this title or section 355(j) (4) (B) of this title shall be extended by a period of six months after the date the patent expires (including any patent extensions).

(c) Market exclusivity for already-marketed drugs

If the Secretary determines that information relating to the use of an approved drug in the pediatric population may produce health benefits in that population and makes a written request to the holder of an approved application under section 355(b) (1) of this title for pediatric studies (which shall include a timeframe for completing such studies), the holder agrees to the request, the studies are completed within any such timeframe, and the reports thereof are submitted in accordance with subsection (d) (2) of this section or accepted in accordance with subsection (d) (3) of this section--

(1) (A) (i) the period referred to in subsection (c) (3) (D) (ii) of section 355 of this title, and in subsection (j) (5) (D) (ii) of such section, is deemed to be five years and six months rather than five years, and the references in subsections (c) (3) (D) (ii) and (j) (5) (D) (ii) of such section to four years, to forty-eight months, and to seven and one-half years are deemed to be four and one-half years, fifty-four months, and eight years, respectively; or

(ii) the period referred to in clauses (iii) and (iv) of subsection (c) (3) (D) of such section, and in clauses (iii) and (iv) of subsection (j) (5) (D) of such section, is deemed to be three years and six months rather than three years; and

(B) if the drug is designated under section 360bb of this title for a rare disease or condition, the period referred to in section 360cc(a) of this title is deemed to be seven years and six months rather than seven years; and

(2) (A) if the drug is the subject of--

(i) a listed patent for which a certification has been submitted under subsection (b) (2) (A) (ii) or (j) (2) (A) (vii) (II) of section 355 of this title and for which pediatric studies were submitted prior to the expiration of the patent (including any patent extensions); or

(ii) a listed patent for which a certification has been submitted under subsection (b) (2) (A) (iii) or (j) (2) (A) (vii) (III) of section 355 of this title,

the period during which an application may not be approved under section 355(c) (3) of this title or section 355(j) (4) (B) of this title shall be extended by a period of six months after the date the patent expires (including any patent extensions); or

(B) if the drug is the subject of a listed patent for which a certification has been submitted under subsection (b) (2) (A) (iv) or (j) (2) (A) (vii) (IV) of section 355 of this title, and in the patent

infringement litigation resulting from the certification the court determines that the patent is valid and would be infringed, the period during which an application may not be approved under section 355(c)(3) of this title or section 355(j)(4)(B) of this title shall be extended by a period of six months after the date the patent expires (including any patent extensions).

(d) Conduct of pediatric studies

(1) Agreement for studies

The Secretary may, pursuant to a written request from the Secretary under subsection (b) or (c) of this section, after consultation with--

(A) the sponsor of an application for an investigational new drug under section 355(i) of this title;

(B) the sponsor of an application for a new drug under section 355(b)(1) of this title; or

(C) the holder of an approved application for a drug under section 355(b)(1) of this title,

agree with the sponsor or holder for the conduct of pediatric studies for such drug. Such agreement shall be in writing and shall include a timeframe for such studies.

(2) Written protocols to meet the studies requirement

If the sponsor or holder and the Secretary agree upon written protocols for the studies, the studies requirement of subsection (b) or (c) of this section is satisfied upon the completion of the studies and submission of the reports thereof in accordance with the original written request and the written agreement referred to in paragraph (1). In reaching an agreement regarding written protocols, the Secretary shall take into account adequate representation of children of ethnic and racial minorities. Not later than 60 days after the submission of the report of the studies, the Secretary shall determine if such studies were or were not conducted in accordance with the original written request and the written agreement and reported in accordance with the requirements of the Secretary for filing and so notify the sponsor or holder.

(3) Other methods to meet the studies requirement

If the sponsor or holder and the Secretary have not agreed in writing on the protocols for the studies, the studies requirement of subsection (b) or (c) of this section is satisfied when such studies have been completed and the reports accepted by the Secretary. Not later than 90 days after the submission of the reports of the studies, the Secretary shall accept or reject such reports and so notify the sponsor or holder. The Secretary's only responsibility in accepting or rejecting the reports shall be to determine, within the 90 days, whether the studies fairly respond to the written request, have been conducted in accordance with commonly accepted scientific principles and protocols, and have been reported in accordance with the requirements of the Secretary for filing.

(4) Written request to holders of approved applications for drugs that have market exclusivity

(A) Request and response

If the Secretary makes a written request for pediatric studies (including neonates, as appropriate) under subsection (c) of this section to the holder of an application approved under section 355(b)(1) of this title, the holder, not later than 180 days after receiving the written request, shall respond to the Secretary as to the intention of the holder to act on the request by--

- (i) indicating when the pediatric studies will be initiated, if the holder agrees to the request; or
- (ii) indicating that the holder does not agree to the request.

(B) No agreement to request

(i) Referral

If the holder does not agree to a written request within the time period specified in subparagraph (A), and if the Secretary determines that there is a continuing need for information relating to the use of the drug in the pediatric population (including neonates, as appropriate), the Secretary shall refer the drug to the Foundation for the National Institutes of Health established under section 290b of title 42 (referred to in this paragraph as the ``Foundation'') for the conduct of the pediatric studies described in the written request.

(ii) Public notice

The Secretary shall give public notice of the name of the drug, the name of the manufacturer, and the indications to be studied made in a referral under clause (i).

(C) Lack of funds

On referral of a drug under subparagraph (B)(i), the Foundation shall issue a proposal to award a grant to conduct the requested studies unless the Foundation certifies to the Secretary, within a timeframe that the Secretary determines is appropriate through guidance, that the Foundation does not have funds available under section 290b(j)(9)(B)(i) \1\ of title 42 to conduct the requested studies. If the Foundation so certifies, the Secretary shall refer the drug for inclusion on the list established under section 284m of title 42 for the conduct of the studies.

\1\ See References in Text note below.

(D) Effect of subsection

Nothing in this subsection (including with respect to referrals from the Secretary to the Foundation) alters or amends section 331(j) of this title or section 552 of title 5 or section 1905 of title 18.

(E) No requirement to refer

Nothing in this subsection shall be construed to require that every declined written request shall be referred to the

Foundation.

(F) Written requests under subsection (b)

For drugs under subsection (b) of this section for which written requests have not been accepted, if the Secretary determines that there is a continuing need for information relating to the use of the drug in the pediatric population (including neonates, as appropriate), the Secretary shall issue a written request under subsection (c) of this section after the date of approval of the drug.

(e) Delay of effective date for certain application

If the Secretary determines that the acceptance or approval of an application under section 355(b)(2) or 355(j) of this title for a new drug may occur after submission of reports of pediatric studies under this section, which were submitted prior to the expiration of the patent (including any patent extension) or the applicable period under clauses (ii) through (iv) of section 355(c)(3)(D) of this title or clauses (ii) through (iv) of section 355(j)(5)(D) of this title, but before the Secretary has determined whether the requirements of subsection (d) of this section have been satisfied, the Secretary shall delay the acceptance or approval under section 355(b)(2) or 355(j) of this title until the determination under subsection (d) of this section is made, but any such delay shall not exceed 90 days. In the event that requirements of this section are satisfied, the applicable six-month period under subsection (b) or (c) of this section shall be deemed to have been running during the period of delay.

(f) Notice of determinations on studies requirement

The Secretary shall publish a notice of any determination that the requirements of subsection (d) of this section have been met and that submissions and approvals under subsection (b)(2) or (j) of section 355 of this title for a drug will be subject to the provisions of this section.

(g) Limitations

A drug to which the six-month period under subsection (b) or (c) of this section has already been applied--

(1) may receive an additional six-month period under subsection (c)(1)(A)(ii) of this section for a supplemental application if all other requirements under this section are satisfied, except that such a drug may not receive any additional such period under subsection (c)(2) of this section; and

(2) may not receive any additional such period under subsection (c)(1)(B) of this section.

(h) Relationship to regulations

Notwithstanding any other provision of law, if any pediatric study is required pursuant to regulations promulgated by the Secretary and such study meets the completeness, timeliness, and other requirements of this section, such study shall be deemed to satisfy the requirement for market exclusivity pursuant to this section.

(i) Labeling supplements

(1) Priority status for pediatric supplements

Any supplement to an application under section 355 of this title proposing a labeling change pursuant to a report on a pediatric study under this section--

- (A) shall be considered to be a priority supplement; and
- (B) shall be subject to the performance goals established by the Commissioner for priority drugs.

(2) Dispute resolution

(A) Request for labeling change and failure to agree

If the Commissioner determines that an application with respect to which a pediatric study is conducted under this section is approvable and that the only open issue for final action on the application is the reaching of an agreement between the sponsor of the application and the Commissioner on appropriate changes to the labeling for the drug that is the subject of the application, not later than 180 days after the date of submission of the application--

- (i) the Commissioner shall request that the sponsor of the application make any labeling change that the Commissioner determines to be appropriate; and
- (ii) if the sponsor of the application does not agree to make a labeling change requested by the Commissioner, the Commissioner shall refer the matter to the Pediatric Advisory Subcommittee of the Anti-Infective Drugs Advisory Committee.

(B) Action by the Pediatric Advisory Subcommittee of the Anti-Infective Drugs Advisory Committee

Not later than 90 days after receiving a referral under subparagraph (A) (ii), the Pediatric Advisory Subcommittee of the Anti-Infective Drugs Advisory Committee shall--

- (i) review the pediatric study reports; and
- (ii) make a recommendation to the Commissioner concerning appropriate labeling changes, if any.

(C) Consideration of recommendations

The Commissioner shall consider the recommendations of the Pediatric Advisory Subcommittee of the Anti-Infective Drugs Advisory Committee and, if appropriate, not later than 30 days after receiving the recommendation, make a request to the sponsor of the application to make any labeling change that the Commissioner determines to be appropriate.

(D) Misbranding

If the sponsor of the application, within 30 days after receiving a request under subparagraph (C), does not agree to make a labeling change requested by the Commissioner, the Commissioner may deem the drug that is the subject of the application to be misbranded.

(E) No effect on authority

Nothing in this subsection limits the authority of the

United States to bring an enforcement action under this chapter when a drug lacks appropriate pediatric labeling. Neither course of action (the Pediatric Advisory Subcommittee of the Anti-Infective Drugs Advisory Committee process or an enforcement action referred to in the preceding sentence) shall preclude, delay, or serve as the basis to stay the other course of action.

(j) Dissemination of pediatric information

(1) In general

Not later than 180 days after the date of submission of a report on a pediatric study under this section, the Commissioner shall make available to the public a summary of the medical and clinical pharmacology reviews of pediatric studies conducted for the supplement, including by publication in the Federal Register.

(2) Effect of subsection

Nothing in this subsection alters or amends section 331(j) of this title or section 552 of title 5 or section 1905 of title 18.

(k) Clarification of interaction of market exclusivity under this section and market exclusivity awarded to an applicant for approval of a drug under section 355(j) of this title

If a 180-day period under section 355(j) (5) (B) (iv) of this title overlaps with a 6-month exclusivity period under this section, so that the applicant for approval of a drug under section 355(j) of this title entitled to the 180-day period under that section loses a portion of the 180-day period to which the applicant is entitled for the drug, the 180-day period shall be extended from--

(1) the date on which the 180-day period would have expired by the number of days of the overlap, if the 180-day period would, but for the application of this subsection, expire after the 6-month exclusivity period; or

(2) the date on which the 6-month exclusivity period expires, by the number of days of the overlap if the 180-day period would, but for the application of this subsection, expire during the six-month exclusivity period.

(l) Prompt approval of drugs under section 355(j) of this title when pediatric information is added to labeling

(1) General rule

A drug for which an application has been submitted or approved under section 355(j) of this title shall not be considered ineligible for approval under that section or misbranded under section 352 of this title on the basis that the labeling of the drug omits a pediatric indication or any other aspect of labeling pertaining to pediatric use when the omitted indication or other aspect is protected by patent or by exclusivity under clause (iii) or (iv) of section 355(j) (5) (D) of this title.

(2) Labeling

Notwithstanding clauses (iii) and (iv) of section 355(j) (5) (D) of this title, the Secretary may require that the labeling of a drug approved under section 355(j) of this title that omits a pediatric

indication or other aspect of labeling as described in paragraph (1) include--

(A) a statement that, because of marketing exclusivity for a manufacturer--

- (i) the drug is not labeled for pediatric use; or
- (ii) in the case of a drug for which there is an additional pediatric use not referred to in paragraph (1), the drug is not labeled for the pediatric use under paragraph (1); and

(B) a statement of any appropriate pediatric contraindications, warnings, or precautions that the Secretary considers necessary.

(3) Preservation of pediatric exclusivity and other provisions

This subsection does not affect--

(A) the availability or scope of exclusivity under this section;

(B) the availability or scope of exclusivity under section 355 of this title for pediatric formulations;

(C) the question of the eligibility for approval of any application under section 355(j) of this title that omits any other conditions of approval entitled to exclusivity under clause (iii) or (iv) of section 355(j) (5) (D) of this title; or

(D) except as expressly provided in paragraphs (1) and (2), the operation of section 355 of this title.

(m) Report

The Secretary shall conduct a study and report to Congress not later than January 1, 2001, based on the experience under the program established under this section. The study and report shall examine all relevant issues, including--

- (1) the effectiveness of the program in improving information about important pediatric uses for approved drugs;
- (2) the adequacy of the incentive provided under this section;
- (3) the economic impact of the program on taxpayers and consumers, including the impact of the lack of lower cost generic drugs on patients, including on lower income patients; and
- (4) any suggestions for modification that the Secretary determines to be appropriate.

(n) Sunset

A drug may not receive any 6-month period under subsection (b) or (c) of this section unless--

- (1) on or before October 1, 2007, the Secretary makes a written request for pediatric studies of the drug;
- (2) on or before October 1, 2007, an application for the drug is accepted for filing under section 355(b) of this title; and
- (3) all requirements of this section are met.

(June 25, 1938, ch. 675, Sec. 505A, as added Pub. L. 105-115, title I, Sec. 111, Nov. 21, 1997, 111 Stat. 2305; amended Pub. L. 107-109, Secs. 2, 4, 5(b)(2), 7-11(a), 18(a), 19, Jan. 4, 2002, 115 Stat. 1408, 1411, 1413-1415, 1423, 1424.)

References in Text

Section 290b(j)(9)(B)(i) of title 42, referred to in subsec. (d)(4)(C), was in the original ``section 499(j)(9)(B)(i)'' and was translated as meaning section 499(j)(9)(B)(i) of the Public Health Service Act to reflect the probable intent of Congress because there is no section 499 of the Federal Food, Drug, and Cosmetic Act and section 499 of the Public Health Service Act relates to the establishment and duties of the National Foundation for Biomedical Research.

Amendments

2002--Subsec. (a). Pub. L. 107-109, Sec. 19(2), (3), redesignated subsec. (g) as (a). Former subsec. (a) redesignated (b).

Subsec. (a)(1)(A). Pub. L. 107-109, Sec. 19(1)(A), (B), substituted ``(j)(5)(D)(ii)'' for ``(j)(4)(D)(ii)'' in two places in cl. (i) and ``(j)(5)(D)'' for ``(j)(4)(D)'' in cl. (ii).

Subsec. (b). Pub. L. 107-109, Sec. 19(2), (3), redesignated subsec. (a) as (b).

Pub. L. 107-109, Sec. 2(1), struck out heading and text of subsec. (b). Text read as follows: ``Not later than 180 days after November 21, 1997, the Secretary, after consultation with experts in pediatric research shall develop, prioritize, and publish an initial list of approved drugs for which additional pediatric information may produce health benefits in the pediatric population. The Secretary shall annually update the list.''

Subsec. (c). Pub. L. 107-109, Sec. 2(2), in introductory provisions, inserted ``determines that information relating to the use of an approved drug in the pediatric population may produce health benefits in that population and'' after ``the Secretary'' and struck out ``concerning a drug identified in the list described in subsection (b) of this section'' after ``such studies)''.

Subsec. (c)(1)(A). Pub. L. 107-109, Sec. 19(1)(A), (B), substituted ``(j)(5)(D)(ii)'' for ``(j)(4)(D)(ii)'' in two places in cl. (i) and ``(j)(5)(D)'' for ``(j)(4)(D)'' in cl. (ii).

Subsec. (d)(1). Pub. L. 107-109, Sec. 19(4), substituted ``subsection (b) or (c)'' for ``subsection (a) or (c)'' in introductory provisions.

Subsec. (d)(2). Pub. L. 107-109, Secs. 18(a), 19(4), substituted ``subsection (b) or (c)'' for ``subsection (a) or (c)'' and inserted ``In reaching an agreement regarding written protocols, the Secretary shall take into account adequate representation of children of ethnic and racial minorities.''' after first sentence.

Subsec. (d)(3). Pub. L. 107-109, Sec. 19(4), substituted ``subsection (b) or (c)'' for ``subsection (a) or (c)''.

Subsec. (d)(4). Pub. L. 107-109, Sec. 4, added par. (4).

Subsec. (e). Pub. L. 107-109, Sec. 19(1)(C), (4), substituted ``section 355(j)(5)(D)'' for ``section 355(j)(4)(D)'' and ``subsection (b) or (c)'' for ``subsection (a) or (c)''.

Subsec. (g). Pub. L. 107-109, Sec. 19(2), (3), (5), redesignated subsec. (h) as (g) and substituted ``subsection (b) or (c)'' for ``subsection (a) or (b)'' in introductory provisions. Former subsec. (g) redesignated (a).

Pub. L. 107-109, Sec. 7, inserted ``(including neonates in appropriate cases)'' after ``pediatric age groups''.

Subsec. (h). Pub. L. 107-109, Sec. 19(2), (3), redesignated subsec. (i) as (h). Former subsec. (h) redesignated (g).

Subsec. (i). Pub. L. 107-109, Sec. 19(2), (3), redesignated subsec. (l) as (i). Former subsec. (i) redesignated (h).

Subsec. (j). Pub. L. 107-109, Sec. 19(2), (3), redesignated subsec.

(m) as (j). Former subsec. (j) redesignated (n).

Pub. L. 107-109, Sec. 8, added subsec. (j) and struck out heading and text of former subsec. (j). Text read as follows: ``A drug may not receive any six-month period under subsection (a) or (c) of this section unless the application for the drug under section 355(b)(1) of this title is submitted on or before January 1, 2002. After January 1, 2002, a drug shall receive a six-month period under subsection (c) of this section if--

``(1) the drug was in commercial distribution as of November 21, 1997;

``(2) the drug was included by the Secretary on the list under subsection (b) of this section as of January 1, 2002;

``(3) the Secretary determines that there is a continuing need for information relating to the use of the drug in the pediatric population and that the drug may provide health benefits in that population; and

``(4) all requirements of this section are met.''

Subsec. (k). Pub. L. 107-109, Sec. 19(2), (3), redesignated subsec. (n) as (k). Former subsec. (k) redesignated (m).

Subsec. (l). Pub. L. 107-109, Sec. 19(2), (3), redesignated subsec. (o) as (l). Former subsec. (l) redesignated (i).

Pub. L. 107-109, Sec. 5(b)(2), added subsec. (l).

Subsec. (m). Pub. L. 107-109, Sec. 19(2), (3), redesignated subsec. (k) as (m). Former subsec. (m) redesignated (j).

Pub. L. 107-109, Sec. 9, added subsec. (m).

Subsec. (n). Pub. L. 107-109, Sec. 19(4), which directed substitution of ``subsection (b) or (c)'' for ``subsection (a) or (c)'' in subsec. (m), was executed by making the substitution in introductory provisions of subsec. (n), to reflect the probable intent of Congress.

Pub. L. 107-109, Sec. 19(2), (3), redesignated subsec. (j) as (n). Former subsec. (n) redesignated (k).

Pub. L. 107-109, Sec. 10, added subsec. (n).

Subsec. (o). Pub. L. 107-109, Sec. 19(2), (3), redesignated subsec. (o) as (l).

Pub. L. 107-109, Sec. 11(a), added subsec. (o).

Effective Date of 2002 Amendment

Pub. L. 107-109, Sec. 11(b), Jan. 4, 2002, 115 Stat. 1416, provided that: ``The amendment made by subsection (a) [amending this section] takes effect on the date of enactment of this Act [Jan. 4, 2002], including with respect to applications under section 505(j) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(j)) that are approved or pending on that date.''

Report on Pediatric Exclusivity Program

Pub. L. 107-109, Sec. 16, Jan. 4, 2002, 115 Stat. 1421, provided that: ``Not later than October 1, 2006, the Comptroller General of the United States, in consultation with the Secretary of Health and Human Services, shall submit to Congress a report that addresses the following issues, using publicly available data or data otherwise available to the Government that may be used and disclosed under applicable law:

``(1) The effectiveness of section 505A of the Federal Food, Drug, and Cosmetic Act [21 U.S.C. 355a] and section 409I of the Public Health Service Act [42 U.S.C. 284m] (as added by this Act) in ensuring that medicines used by children are tested and properly labeled, including--

``(A) the number and importance of drugs for children that are being tested as a result of this legislation and the importance for children, health care providers, parents, and others of labeling changes made as a result of such testing;

``(B) the number and importance of drugs for children that are not being tested for their use notwithstanding the provisions of this legislation, and possible reasons for the lack of testing; and

``(C) the number of drugs for which testing is being done, exclusivity granted, and labeling changes required, including the date pediatric exclusivity is granted and the date labeling changes are made and which labeling changes required the use of the dispute resolution process established pursuant to the amendments made by this Act [see Short Title of 2002 Amendment note set out under section 301 of this title], together with a description of the outcomes of such process, including a description of the disputes and the recommendations of the Pediatric Advisory Subcommittee of the Anti-Infective Drugs Advisory Committee.

``(2) The economic impact of section 505A of the Federal Food, Drug, and Cosmetic Act and section 409I of the Public Health Service Act (as added by this Act), including an estimate of--

``(A) the costs to taxpayers in the form of higher expenditures by medicaid and other Government programs;

``(B) sales for each drug during the 6-month period for which exclusivity is granted, as attributable to such exclusivity;

``(C) costs to consumers and private insurers as a result of any delay in the availability of lower cost generic equivalents of drugs tested and granted exclusivity under the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 301 et seq.), and loss of revenue by the generic drug industry and retail pharmacies as a result of any such delay; and

``(D) the benefits to the government, to private insurers, and to consumers resulting from decreased health care costs, including--

``(i) decreased hospitalizations and fewer medical errors, due to more appropriate and more effective use of medications in children as a result of testing and re-labeling because of the amendments made by this Act;

``(ii) direct and indirect benefits associated with fewer physician visits not related to hospitalization;

``(iii) benefits to children from missing less time at school and being less affected by chronic illnesses, thereby allowing a better quality of life;

``(iv) benefits to consumers from lower health insurance premiums due to lower treatment costs and hospitalization rates; and

``(v) benefits to employers from reduced need for employees to care for family members.

``(3) The nature and type of studies in children for each drug granted exclusivity under the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 301 et seq.), including--

``(A) a description of the complexity of the studies;

``(B) the number of study sites necessary to obtain appropriate data;

``(C) the number of children involved in any clinical studies; and

``(D) the estimated cost of each of the studies.

``(4) Any recommendations for modifications to the programs

established under section 505A of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355a) and section 409I of the Public Health Service Act [42 U.S.C. 284m] (as added by section 3) that the Secretary determines to be appropriate, including a detailed rationale for each recommendation.

``(5) The increased private and Government-funded pediatric research capability associated with this Act and the amendments made by this Act.

``(6) The number of written requests and additional letters of recommendation that the Secretary issues.

``(7) The prioritized list of off-patent drugs for which the Secretary issues requests.

``(8) (A) The efforts made by the Secretary to increase the number of studies conducted in the neonate population; and

``(B) the results of those efforts, including efforts made to encourage the conduct of appropriate studies in neonates by companies with products that have sufficient safety and other information to make the conduct of studies ethical and safe.''

Study by General Accounting Office

Pub. L. 107-109, Sec. 18(b), Jan. 4, 2002, 115 Stat. 1423, provided that:

``(1) In general.--The Comptroller General of the United States shall conduct a study for the purpose of determining the following:

``(A) The extent to which children of ethnic and racial minorities are adequately represented in studies under section 505A of the Federal Food, Drug, and Cosmetic Act [21 U.S.C. 355a]; and to the extent ethnic and racial minorities are not adequately represented, the reasons for such under representation and recommendations to increase such representation.

``(B) Whether the Food and Drug Administration has appropriate management systems to monitor the representation of the children of ethnic and racial minorities in such studies.

``(C) Whether drugs used to address diseases that disproportionately affect racial and ethnic minorities are being studied for their safety and effectiveness under section 505A of the Federal Food, Drug, and Cosmetic Act.

``(2) Date certain for completing study.--Not later than January 10, 2003, the Comptroller General shall complete the study required in paragraph (1) and submit to the Congress a report describing the findings of the study.''

Section Referred to in Other Sections

This section is referred to in section 355b of this title; title 42 sections 284m, 290b.

PART 320—BIOAVAILABILITY AND BIOEQUIVALENCE REQUIREMENTS

Subpart A—General Provisions

Sec.

320.1 Definitions.

Subpart B—Procedures for Determining the Bioavailability or Bioequivalence of Drug Products

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- 320.63 Retention of bioequivalence samples.

AUTHORITY: 21 U.S.C. 321, 351, 352, 355, 371.

Subpart A—General Provisions

§ 320.1 Definitions.

(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.

[42 FR 1634, Jan. 7, 1977, as amended at 42 FR 1648, Jan. 7, 1977; 57 FR 17997, Apr. 28, 1992; 67 FR 77672, Dec. 19, 2002]

Subpart B—Procedures for Determining the Bioavailability or Bioequivalence of Drug Products

SOURCE: 42 FR 1648, Jan. 7, 1977, unless otherwise noted.

§ 320.21 Requirements for submission of in vivo bioavailability and bioequivalence data.

(a) Any person submitting a full new drug application to the Food and Drug Administration (FDA) shall include in the application either:

(1) Evidence measuring the in vivo bioavailability of the drug product that is the subject of the application; or

(2) Information to permit FDA to waive the submission of evidence measuring in vivo bioavailability.

(b) Any person submitting an abbreviated new drug application to FDA shall include in the application either:

(1) Evidence demonstrating that the drug product that is the subject of the abbreviated new drug application is bioequivalent to the reference listed drug (defined in § 314.3(b) of this chapter); or

(2) Information to show that the drug product is bioequivalent to the reference listed drug which would permit

FDA to waive the submission of evidence demonstrating in vivo bioequivalence as provided in paragraph (f) of this section.

(c) Any person submitting a supplemental application to FDA shall include in the supplemental application the evidence or information set forth in paragraphs (a) and (b) of this section if the supplemental application proposes any of the following changes:

(1) A change in the manufacturing site or a change in the manufacturing process, including a change in product formulation or dosage strength, beyond the variations provided for in the approved application.

(2) A change in the labeling to provide for a new indication for use of the drug product, if clinical studies are required to support the new indication for use.

(3) A change in the labeling to provide for a new dosage regimen or for an additional dosage regimen for a special patient population, e.g., infants, if clinical studies are required to support the new or additional dosage regimen.

(d) FDA may approve a full new drug application, or a supplemental application proposing any of the changes set forth in paragraph (c) of this section, that does not contain evidence of in vivo bioavailability or information to permit waiver of the requirement for in vivo bioavailability data, if all of the following conditions are met.

(1) The application is otherwise approvable.

(2) The application agrees to submit, within the time specified by FDA, either:

(i) Evidence measuring the in vivo bioavailability and demonstrating the in vivo bioequivalence of the drug product that is the subject of the application; or

(ii) Information to permit FDA to waive measurement of in vivo bioavailability.

(e) Evidence measuring the in vivo bioavailability and demonstrating the in vivo bioequivalence of a drug product shall be obtained using one of the approaches for determining bioavailability set forth in § 320.24.

(f) Information to permit FDA to waive the submission of evidence measuring the in vivo bioavailability or

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) 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.

[57 FR 17999, Apr. 28, 1992, as amended at 67 FR 77673, Dec. 19, 2002]

§ 320.24 Types of evidence to measure bioavailability or establish bioequivalence.

(a) Bioavailability may be measured or bioequivalence may be demonstrated by several in vivo and in vitro methods. FDA may require in vivo or in vitro testing, or both, to measure the bioavailability of a drug product or establish the bioequivalence of specific drug products. Information on bioequivalence requirements for specific products is included in the current edition of FDA's publication "Approved Drug Products with Therapeutic Equivalence Evaluations" and any current supplement to the publication. The selection of the method used to meet an in vivo or in vitro testing requirement depends upon the purpose

of the study, the analytical methods available, and the nature of the drug product. Applicants shall conduct bioavailability and bioequivalence testing using the most accurate, sensitive, and reproducible approach available among those set forth in paragraph (b) of this section. The method used must be capable of measuring bioavailability or establishing bioequivalence, as appropriate, for the product being tested.

(b) The following in vivo and in vitro approaches, in descending order of accuracy, sensitivity, and reproducibility, are acceptable for determining the bioavailability or bioequivalence of a drug product.

(1)(i) An in vivo test in humans in which the concentration of the active ingredient or active moiety, and, when appropriate, its active metabolite(s), in whole blood, plasma, serum, or other appropriate biological fluid is measured as a function of time. This approach is particularly applicable to dosage forms intended to deliver the active moiety to the bloodstream for systemic distribution within the body; or

(ii) An in vitro test that has been correlated with and is predictive of human in vivo bioavailability data; or

(2) An in vivo test in humans in which the urinary excretion of the active moiety, and, when appropriate, its active metabolite(s), are measured as a function of time. The intervals at which measurements are taken should ordinarily be as short as possible so that the measure of the rate of elimination is as accurate as possible. Depending on the nature of the drug product, this approach may be applicable to the category of dosage forms described in paragraph (b)(1)(i) of this section. This method is not appropriate where urinary excretion is not a significant mechanism of elimination.

(3) An in vivo test in humans in which an appropriate acute pharmacological effect of the active moiety, and, when appropriate, its active metabolite(s), are measured as a function of time if such effect can be measured with sufficient accuracy, sensitivity, and reproducibility. This approach is applicable to the category of dosage forms described in paragraph (b)(1)(i) of this section only when appropriate

methods are not available for measurement of the concentration of the moiety, and, when appropriate, its active metabolite(s), in biological fluids or excretory products but a method is available for the measurement of an appropriate acute pharmacological effect. This approach may be particularly applicable to dosage forms that are not intended to deliver the active moiety to the bloodstream for systemic distribution.

(4) Well-controlled clinical trials that establish the safety and effectiveness of the drug product, for purposes of measuring bioavailability, or appropriately designed comparative clinical trials, for purposes of demonstrating bioequivalence. This approach is the least accurate, sensitive, and reproducible of the general approaches for measuring bioavailability or demonstrating bioequivalence. For dosage forms intended to deliver the active moiety to the bloodstream for systemic distribution, this approach may be considered acceptable only when analytical methods cannot be developed to permit use of one of the approaches outlined in paragraphs (b)(1)(i) and (b)(2) of this section, when the approaches described in paragraphs (b)(1)(ii), (b)(1)(iii), and (b)(3) of this section are not available. This approach may also be considered sufficiently accurate for measuring bioavailability or demonstrating bioequivalence of dosage forms intended to deliver the active moiety locally, e.g., topical preparations for the skin, eye, and mucous membranes; oral dosage forms not intended to be absorbed, e.g., an antacid or radiopaque medium; and bronchodilators administered by inhalation if the onset and duration of pharmacological activity are defined.

(5) A currently available *in vitro* test acceptable to FDA (usually a dissolution rate test) that ensures human *in vivo* bioavailability.

(6) Any other approach deemed adequate by FDA to measure bioavailability or establish bioequivalence.

(c) FDA may, notwithstanding prior requirements for measuring bioavailability or establishing bioequivalence, require *in vivo* testing in hu-

mans of a product at any time if the agency has evidence that the product:

(1) May not produce therapeutic effects comparable to a pharmaceutical equivalent or alternative with which it is intended to be used interchangeably;

(2) May not be bioequivalent to a pharmaceutical equivalent or alternative with which it is intended to be used interchangeably; or

(3) Has greater than anticipated potential toxicity related to pharmacokinetic or other characteristics.

[57 FR 17999, Apr. 28, 1992; 57 FR 29354, July 1, 1992, as amended at 67 FR 77673, Dec. 19, 2002]

§ 320.25 Guidelines for the conduct of an *in vivo* bioavailability study.

(a) *Guiding principles.* (1) The basic principle in an *in vivo* bioavailability study is that no unnecessary human research should be done.

(2) An *in vivo* bioavailability study is generally done in a normal adult population under standardized conditions. In some situations, an *in vivo* bioavailability study in humans may preferably and more properly be done in suitable patients. Critically ill patients shall not be included in an *in vivo* bioavailability study unless the attending physician determines that there is a potential benefit to the patient.

(b) *Basic design.* The basic design of an *in vivo* bioavailability study is determined by the following:

(1) The scientific questions to be answered.

(2) The nature of the reference material and the dosage form to be tested.

(3) The availability of analytical methods.

(4) Benefit-risk considerations in regard to testing in humans.

(c) *Comparison to a reference material.* *In vivo* bioavailability testing of a drug product shall be in comparison to an appropriate reference material unless some other approach is more appropriate for valid scientific reasons.

(d) *Previously unmarketed active drug ingredients or therapeutic moieties.* (1) An *in vivo* bioavailability study involving a drug product containing an active drug ingredient or therapeutic moiety that has not been approved for marketing can be used to measure the following pharmacokinetic data:

demonstrating the in vivo bioequivalence shall meet the criteria set forth in § 320.22.

(g) Any person holding an approved full or abbreviated new drug application shall submit to FDA a supplemental application containing new evidence measuring the in vivo bioavailability or demonstrating the in vivo bioequivalence of the drug product that is the subject of the application if notified by FDA that:

(1) There are data demonstrating that the dosage regimen in the labeling is based on incorrect assumptions or facts regarding the pharmacokinetics of the drug product and that following this dosage regimen could potentially result in subtherapeutic or toxic levels; or

(2) There are data measuring significant intra-batch and batch-to-batch variability, e.g., plus or minus 25 percent, in the bioavailability of the drug product.

(h) The requirements of this section regarding the submission of evidence measuring the in vivo bioavailability or demonstrating the in vivo bioequivalence apply only to a full or abbreviated new drug application or a supplemental application for a finished dosage formulation.

[57 FR 17998, Apr. 28, 1992, as amended at 67 FR 77672, Dec. 19, 2002]

§ 320.22 Criteria for waiver of evidence of in vivo bioavailability or bioequivalence.

(a) Any person submitting a full or abbreviated new drug application, or a supplemental application proposing any of the changes set forth in § 320.21(c), may request FDA to waive the requirement for the submission of evidence measuring the in vivo bioavailability or demonstrating the in vivo bioequivalence of the drug product that is the subject of the application. An applicant shall submit a request for waiver with the application. Except as provided in paragraph (f) of this section, FDA shall waive the requirement for the submission of evidence of in vivo bioavailability or bioequivalence if the drug product meets any of the provisions of paragraphs (b), (c), (d), or (e) of this section.

(b) For certain drug products, the in vivo bioavailability or bioequivalence of the drug product may be self-evident. FDA shall waive the requirement for the submission of evidence obtained in vivo measuring the bioavailability or demonstrating the bioequivalence of these drug products. A drug product's in vivo bioavailability or bioequivalence may be considered self-evident based on other data in the application if the product meets one of the following criteria:

(1) The drug product:

(i) Is a parenteral solution intended solely for administration by injection, or an ophthalmic or otic solution; and

(ii) Contains the same active and inactive ingredients in the same concentration as a drug product that is the subject of an approved full new drug application or abbreviated new drug application.

(2) The drug product:

(i) Is administered by inhalation as a gas, e.g., a medicinal or an inhalation anesthetic; and

(ii) Contains an active ingredient in the same dosage form as a drug product that is the subject of an approved full new drug application or abbreviated new drug application.

(3) The drug product:

(i) Is a solution for application to the skin, an oral solution, elixir, syrup, tincture, a solution for aerosolization or nebulization, a nasal solution, or similar other solubilized form; and

(ii) Contains an active drug ingredient in the same concentration and dosage form as a drug product that is the subject of an approved full new drug application or abbreviated new drug application; and

(iii) Contains no inactive ingredient or other change in formulation from the drug product that is the subject of the approved full new drug application or abbreviated new drug application that may significantly affect absorption of the active drug ingredient or active moiety for products that are systemically absorbed, or that may significantly affect systemic or local availability for products intended to act locally.

(c) FDA shall waive the requirement for the submission of evidence measuring the in vivo bioavailability or

demonstrating the in vivo bioequivalence of a solid oral dosage form (other than a delayed release or extended release dosage form) of a drug product determined to be effective for at least one indication in a Drug Efficacy Study Implementation notice or which is identical, related, or similar to such a drug product under §310.6 of this chapter unless FDA has evaluated the drug product under the criteria set forth in §320.33, included the drug product in the Approved Drug Products with Therapeutic Equivalence Evaluations List, and rated the drug product as having a known or potential bioequivalence problem. A drug product so rated reflects a determination by FDA that an in vivo bioequivalence study is required.

(d) For certain drug products, bioavailability may be measured or bioequivalence may be demonstrated by evidence obtained in vitro in lieu of in vivo data. FDA shall waive the requirement for the submission of evidence obtained in vivo measuring the bioavailability or demonstrating the bioequivalence of the drug product if the drug product meets one of the following criteria:

(1) [Reserved]

(2) The drug product is in the same dosage form, but in a different strength, and is proportionally similar in its active and inactive ingredients to another drug product for which the same manufacturer has obtained approval and the conditions in paragraphs (d)(2)(i) through (d)(2)(iii) of this section are met:

(i) The bioavailability of this other drug product has been measured;

(ii) Both drug products meet an appropriate in vitro test approved by FDA; and

(iii) The applicant submits evidence showing that both drug products are proportionally similar in their active and inactive ingredients.

(iv) Paragraph (d) of this section does not apply to delayed release or extended release products.

(3) The drug product is, on the basis of scientific evidence submitted in the application, shown to meet an in vitro test that has been correlated with in vivo data.

(4) The drug product is a reformulated product that is identical, except for a different color, flavor, or preservative that could not affect the bioavailability of the reformulated product, to another drug product for which the same manufacturer has obtained approval and the following conditions are met:

(i) The bioavailability of the other product has been measured; and

(ii) Both drug products meet an appropriate in vitro test approved by FDA.

(e) FDA, for good cause, may waive a requirement for the submission of evidence of in vivo bioavailability or bioequivalence if waiver is compatible with the protection of the public health. For full new drug applications, FDA may defer a requirement for the submission of evidence of in vivo bioavailability if deferral is compatible with the protection of the public health.

(f) FDA, for good cause, may require evidence of in vivo bioavailability or bioequivalence for any drug product if the agency determines that any difference between the drug product and a listed drug may affect the bioavailability or bioequivalence of the drug product.

[57 FR 17998, Apr. 28, 1992, as amended at 67 FR 77673, Dec. 19, 2002]

§ 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 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 shall be of sufficient sensitivity to detect

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substance and, therefore, will not result in the introduction of any substance into the environment.

(f) Extramural contracts, other agreements, and grants for research for such purposes as to develop analytical methods or other test methodologies.

(g) Activities of voluntary Federal-State cooperative programs, including issuance of model regulations proposed for State adoption.

(h) Issuance, amendment, or revocation of procedural or administrative regulations and guidance documents, including procedures for submission of applications for product development, testing and investigational use, and approval.

(i) Corrections and technical changes in regulations.

(j) Issuance of CGMP regulations, HACCP regulations, establishment standards, emergency permit control regulations, GLP regulations, and issuance or denial of permits, exemptions, variances, or stays under these regulations.

(k) Establishment or repeal by regulation of labeling requirements for marketed articles if there will be no increase in the existing levels of use or change in the intended uses of the product or its substitutes.

(l) Routine maintenance and minor construction activities such as:

(1) Repair to or replacement of equipment or structural components (e.g., door, roof, or window) of facilities controlled by FDA;

(2) Lease extensions, renewals, or succeeding leases;

(3) Construction or lease construction of 10,000 square feet or less of occupiable space;

(4) Relocation of employees into existing owned or currently leased space;

(5) Acquisition of 20,000 square feet or less of occupiable space in a structure that was substantially completed before the issuance of solicitation for offers; and

(6) Acquisition of between 20,000 square feet and 40,000 square feet of occupiable space if it constitutes less than 40 percent of the occupiable space in a structure that was substantially completed before the solicitation for offers.

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(m) Disposal of low-level radioactive waste materials (as defined in the Nuclear Regulatory Commission regulations at 10 CFR 61.2) and chemical waste materials generated in the laboratories serviced by the contracts administered by FDA, if the waste is disposed of in compliance with all applicable Federal, State, and local requirements.

[62 FR 40592, July 29, 1997, as amended at 65 FR 56479, Sept. 19, 2000]

§ 25.31 Human drugs and biologics.

The classes of actions listed in this section are categorically excluded and, therefore, ordinarily do not require the preparation of an EA or an EIS:

(a) Action on an NDA, abbreviated application, application for marketing approval of a biologic product, or a supplement to such applications, or action on an OTC monograph, if the action does not increase the use of the active moiety.

(b) Action on an NDA, abbreviated application, or a supplement to such applications, or action on an OTC monograph, if the action increases the use of the active moiety, but the estimated concentration of the substance at the point of entry into the aquatic environment will be below 1 part per billion.

(c) Action on an NDA, abbreviated application, application for marketing approval of a biologic product, or a supplement to such applications, or action on an OTC monograph, for substances that occur naturally in the environment when the action does not alter significantly the concentration or distribution of the substance, its metabolites, or degradation products in the environment.

(d) Withdrawal of approval of an NDA or an abbreviated application.

(e) Action on an IND.

(f) Testing and release by the Center for Biologics Evaluation and Research of lots or batches of a licensed biologic product.

(g) Establishment of bioequivalence requirements for a human drug or a comparability determination for a biologic product subject to licensing.

(h) Issuance, revocation, or amendment of a standard for a biologic product.

(i) Revocation of a license for a biologic product.

(j) Action on an application for marketing approval for marketing of a biologic product for transfusable human blood or blood components and plasma.

[62 FR 40592, July 29, 1997, as amended at 63 FR 26697, May 13, 1998; 64 FR 399, Jan. 5, 1999]

§ 25.32 Foods, food additives, and color additives.

The classes of actions listed in this section are categorically excluded and, therefore, ordinarily do not require the preparation of an EA or an EIS:

(a) Issuance, amendment, or repeal of a food standard.

(b) Action on a request for exemption for investigational use of a food additive if the food additive to be shipped under the request is intended to be used for clinical studies or research.

(c) Approval of a color additive petition to change a provisionally listed color additive to permanent listing for use in food, drugs, devices, or cosmetics.

(d) Testing and certification of batches of a color additive.

(e) Issuance of an interim food additive regulation.

(f) Affirmation of a food substance as GRAS for humans or animals on FDA's initiative or in response to a petition, under parts 182, 184, 186, or 582 of this chapter, and establishment or amendment of a regulation for a prior-sanctioned food ingredient, as defined in §§ 170.3(l) and 181.5(a) of this chapter, if the substance or food ingredient is already marketed in the United States for the proposed use.

(g) Issuance and enforcement of regulations relating to the control of communicable diseases or to interstate conveyance sanitation under parts 1240 and 1250 of this chapter.

(h) Approval of a request for diversion of adulterated or misbranded food for humans or animals to use as animal feeds.

(i) Approval of a food additive petition or GRAS affirmation petition, the granting of a request for exemption from regulation as a food additive under § 170.39 of this chapter, or allowing a notification submitted under 21 U.S.C. 348(h) to become effective, when the substance is present in finished

food-packaging material at not greater than 5 percent-by-weight and is expected to remain with finished food-packaging material through use by consumers or when the substance is a component of a coating of a finished food-packaging material.

(j) Approval of a food additive petition or GRAS affirmation petition, the granting of a request for exemption from regulation as a food additive under § 170.39 of this chapter, or allowing a notification submitted under 21 U.S.C. 348(h) to become effective, when the substance is to be used as a component of a food-contact surface of permanent or semipermanent equipment or of another food-contact article intended for repeated use.

(k) Approval of a food additive petition, color additive petition, or GRAS affirmation petition, or allowing a notification submitted under 21 U.S.C. 348(h) to become effective, for substances added directly to food that are intended to remain in food through ingestion by consumers and that are not intended to replace macronutrients in food.

(l) Approval of a petition for color additives used in contact lenses, sutures, filaments used as supporting haptics in intraocular lenses, bone cement, and in other FDA-regulated products having similarly low levels of use.

(m) Action to prohibit or otherwise restrict or reduce the use of a substance in food, food packaging, or cosmetics.

(n) Issuance, amendment, or revocation of a regulation pertaining to infant formulas.

(o) Approval of a food additive petition for the intended expression product(s) present in food derived from new plant varieties.

(p) Issuance, amendment, or revocation of a regulation in response to a reference amount petition as described in § 101.12(h) of this chapter, a nutrient content claim petition as described in § 101.69 of this chapter, a health claim petition as described in § 101.70 of this chapter, or a petition pertaining to the label declaration of ingredients as described in § 101.103 of this chapter.