FDA HUMAN RESEARCH REGULATIONS

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Subpart A—General Provisions

§11.1 Scope.
(a) The regulations in this part set forth the criteria under which the agency considers electronic records, electronic signatures, and handwritten signatures executed to electronic records to be trustworthy, reliable, and generally equivalent to paper records and handwritten signatures executed on paper.
(b) This part applies to records in electronic form that are created, modified, maintained, archived, retrieved, or transmitted, under any records requirements set forth in agency regulations. This part also applies to electronic records submitted to the agency under requirements of the Federal Food, Drug, and Cosmetic Act and the Public Health Service Act, even if such records are not specifically identified in agency regulations. However, this part does not apply to paper records that are, or have been, transmitted by electronic means.
(c) Where electronic signatures and their associated electronic records meet the requirements of this part, the agency will consider the electronic signatures to be equivalent to full hand-written signatures, initials, and other general signings as required by agency regulations, unless specifically excepted by regulation(s) effective on or after August 20, 1997.
(d) Electronic records that meet the requirements of this part may be used in lieu of paper records, in accordance with §11.2, unless paper records are specifically required.
(e) Computer systems (including hardware and software), controls, and attendant documentation maintained under this part shall be readily available for, and subject to, FDA inspection.

§11.2 Implementation.
(a) For records required be maintaining but not submitting to the agency, persons may use electronic records in lieu of paper records or electronic signatures in lieu of traditional signatures, in whole or in part, provided that the requirements of this part are met.
(b) For records submitted to the agency, persons may use electronic records in lieu of paper records or electronic signatures in lieu of traditional signatures, in whole or in part, provided that:
   (1) The requirements of this part are met; and
   (2) The document or parts of a document to be submitted have been identified in public docket No. 92S–0251 as being the type of submission the agency accepts in electronic form. This docket will identify specifically what types of documents or parts of documents are acceptable for submission in electronic form without paper records and the agency receiving unit(s) (e.g., specific
center, office, division, branch) to which such submissions may be made. Documents to agency receiving unit(s) not specified in the public docket will not be considered as official if they are submitted in electronic form; paper forms of such documents will be considered as official and must accompany any electronic records. Persons are expected to consult with the intended agency receiving unit for details on how (e.g., method of transmission, media, file formats, and technical protocols) and whether to proceed with the electronic submission.

§11.3 Definitions.
(a) The definitions and interpretations of terms contained in section 201 of the act apply to those terms when used in this part.
(b) The following definitions of terms also apply to this part:
   (2) Agency means the Food and Drug Administration.
   (3) Biometrics means a method of verifying an individual’s identity based on measurement of the individual’s physical feature(s) or repeatable action(s) where those features and/or actions are both unique to that individual and measurable.
   (4) Closed system means an environment in which system access is controlled by persons who are responsible for the content of electronic records that are on the system.
   (5) Digital signature means an electronic signature based upon cryptographic methods of originator authentication, computed by using a set of rules and a set of parameters such that the identity of the signer and the integrity of the data can be verified.
   (6) Electronic record means any combination of text, graphics, data, audio, pictorial, or other information representation in digital form that is created, modified, maintained, archived, retrieved, or distributed by a computer system.
   (7) Electronic signature means a computer data compilation of any symbol or series of symbols executed, adopted, or authorized by an individual to be the legally binding equivalent of the individual’s handwritten signature.
   (8) Handwritten signature means the scripted name or legal mark of an individual handwritten by that individual and executed or adopted with the present intention to authenticate a writing in a permanent form. The act of signing with a writing or marking instrument such as a pen or stylus is preserved. The scripted name or legal mark, while conventionally applied to paper, may also be applied to other devices that capture the name or mark.
   (9) Open system means an environment in which system access is not controlled by persons who are responsible for the content of electronic records that are on the system.
Subpart B—Electronic Records

§11.10 Controls for closed systems.

Persons who use closed systems to create, modify, maintain, or transmit electronic records shall employ procedures and controls designed to ensure the authenticity, integrity, and, when appropriate, the confidentiality of electronic records, and to ensure that the signer cannot readily repudiate the signed record as not genuine. Such procedures and controls shall include the following:

(a) Validation of systems to ensure accuracy, reliability, consistent intended performance, and the ability to discern invalid or altered records.

(b) The ability to generate accurate and complete copies of records in both human readable and electronic form suitable for inspection, review, and copying by the agency. Persons should contact the agency if there are any questions regarding the ability of the agency to perform such review and copying of the electronic records.

(c) Protection of records to enable their accurate and ready retrieval throughout the records retention period.

(d) Limiting system access to authorized individuals.

(e) Use of secure, computer-generated, time-stamped audit trails to independently record the date and time of operator entries and actions that create, modify, or delete electronic records. Record changes shall not obscure previously recorded information. Such audit trail documentation shall be retained for a period at least as long as that required for the subject electronic records and shall be available for agency review and copying.

(f) Use of operational system checks to enforce permitted sequencing of steps and events, as appropriate.

(g) Use of authority checks to ensure that only authorized individuals can use the system, electronically sign a record, access the operation or computer system input or output device, alter a record, or perform the operation at hand.

(h) Use of device (e.g., terminal) checks to determine, as appropriate, the validity of the source of data input or operational instruction.

(i) Determination that persons who develop, maintain, or use electronic record/electronic signature systems have the education, training, and experience to perform their assigned tasks.

(j) The establishment of, and adherence to, written policies that hold individuals accountable and responsible for actions initiated under their electronic signatures, in order to deter record and signature falsification.

(k) Use of appropriate controls over systems documentation including:

(1) Adequate controls over the distribution of, access to, and use of documentation for system operation and maintenance.

(2) Revision and change control procedures to maintain an audit trail that documents time-sequenced development and modification of systems documentation.

§11.30 Controls for open systems.

Persons who use open systems to create, modify, maintain, or transmit electronic records shall employ procedures and controls designed to ensure the authenticity, integrity, and, as appropriate, the confidentiality of electronic records from the point of their creation to
the point of their receipt. Such procedures and controls shall include those identified in §11.10, as appropriate, and additional measures such as document encryption and use of appropriate digital signature standards to ensure, as necessary under the circumstances, record authenticity, integrity, and confidentiality.

§11.50 Signature manifestations.
(a) Signed electronic records shall contain information associated with the signing that clearly indicates all of the following:
   (1) The printed name of the signer;
   (2) The date and time when the signature was executed; and
   (3) The meaning (such as review, approval, responsibility, or authorship) associated with the signature.
(b) The items identified in paragraphs (a)(1), (a)(2), and (a)(3) of this section shall be subject to the same controls as for electronic records and shall be included as part of any human readable form of the electronic record (such as electronic display or printout).

§11.70 Signature/record linking.
Electronic signatures and handwritten signatures executed to electronic records shall be linked to their respective electronic records to ensure that the signatures cannot be excised, copied, or otherwise transferred to falsify an electronic record by ordinary means.

Subpart C—Electronic Signatures

§11.100 General requirements.
(a) Each electronic signature shall be unique to one individual and shall not be reused by, or reassigned to, anyone else.
(b) Before an organization establishes, assigns, certifies, or otherwise sanctions an individual’s electronic signature, or any element of such electronic signature, the organization shall verify the identity of the individual.
(c) Persons using electronic signatures shall, prior to or at the time of such use, certify to the agency that the electronic signatures in their system, used on or after August 20, 1997, are intended to be the legally binding equivalent of traditional handwritten signatures.
   (1) The certification shall be submitted in paper form and signed with a traditional handwritten signature, to the Office of Regional Operations (HFC–100), 5600 Fishers Lane, Rockville, MD 20857.
   (2) Persons using electronic signatures shall, upon agency request, provide additional certification or testimony that a specific electronic signature is the legally binding equivalent of the signer’s handwritten signature.

§11.200 Electronic signature components and controls.
(a) Electronic signatures that are not based upon biometrics shall:
   (1) Employ at least two distinct identification components such as an identification code and password.
(i) When an individual executes a series of signings during a single, continuous period of controlled system access, the first signing shall be executed using all electronic signature components; subsequent signings shall be executed using at least one electronic signature component that is only executable by, and designed to be used only by, the individual.

(ii) When an individual executes one or more signings not performed during a single, continuous period of controlled system access, each signing shall be executed using all of the electronic signature components.

(2) Be used only by their genuine owners; and

(3) Be administered and executed to ensure that attempted use of an individual’s electronic signature by anyone other than its genuine owner requires collaboration of two or more individuals.

(b) Electronic signatures based upon biometrics shall be designed to ensure that they cannot be used by anyone other than their genuine owners.

 §11.300 Controls for identification codes/passwords.

Persons who use electronic signatures based upon use of identification codes in combination with passwords shall employ controls to ensure their security and integrity. Such controls shall include:

(a) Maintaining the uniqueness of each combined identification code and password, such that no two individuals have the same combination of identification code and password.

(b) Ensuring that identification code and password issuances are periodically checked, recalled, or revised (e.g., to cover such events as password aging).

(c) Following loss management procedures to electronically de-authorize lost, stolen, missing, or otherwise potentially compromised tokens, cards, and other devices that bear or generate identification code or password information, and to issue temporary or permanent replacements using suitable, rigorous controls.

(d) Use of transaction safeguards to prevent unauthorized use of passwords and/or identification codes, and to detect and report in an immediate and urgent manner any attempts at their unauthorized use to the system security unit, and, as appropriate, to organizational management.

(e) Initial and periodic testing of devices, such as tokens or cards, that bear or generate identification code or password information to ensure that they function properly and have not been altered in an unauthorized manner.
21 CFR 50 PROTECTION OF HUMAN SUBJECTS
[Revised as of April 1, 2002]

Subpart A--General Provisions

§50.1 Scope.
(a) This part applies to all clinical investigations regulated by the Food and Drug Administration under sections 505(i) and 520(g) of the Federal Food, Drug, and Cosmetic Act, as well as clinical investigations that support applications for research or marketing permits for products regulated by the Food and Drug Administration, including foods, including dietary supplements, that bear a nutrient content claim or a health claim, infant formulas, food and color additives, drugs for human use, medical devices for human use, biological products for human use, and electronic products. Additional specific obligations and commitments of, and standards of conduct for, persons who sponsor or monitor clinical investigations involving particular test articles may also be found in other parts (e.g., parts 312 and 812). Compliance with these parts is intended to protect the rights and safety of subjects involved in investigations filed with the Food and Drug Administration pursuant to sections 403, 406, 409, 412, 413, 502, 503, 505, 510, 513-516, 518-520, 721, and 801 of the Federal Food, Drug, and Cosmetic Act and sections 351 and 354-360F of the Public Health Service Act.
(b) References in this part to regulatory sections of the Code of Federal Regulations are to chapter I of title 21, unless otherwise noted.

§50.3 Definitions.
As used in this part:
(b) Application for research or marketing permit includes:
(1) A color additive petition, described in part 71.
(2) A food additive petition, described in parts 171 and 571.
(3) Data and information about a substance submitted as part of the procedures for establishing that the substance is generally recognized as safe for use that results or may reasonably be expected to result, directly or indirectly, in its becoming a component or otherwise affecting the characteristics of any food, described in §§170.30 and 570.30.
(4) Data and information about a food additive submitted as part of the procedures for food additives permitted to be used on an interim basis pending additional study, described in §180.1.
(5) Data and information about a substance submitted as part of the procedures for establishing a tolerance for unavoidable contaminants in food and food-packaging materials, described in section 406 of the act.
(6) An investigational new drug application, described in part 312 of this chapter.
(7) A new drug application, described in part 314.
(8) Data and information about the bioavailability or bioequivalence of drugs for human use submitted as part of the procedures for issuing, amending, or repealing a bioequivalence requirement, described in part 320.

(9) Data and information about an over-the-counter drug for human use submitted as part of the procedures for classifying these drugs as generally recognized as safe and effective and not misbranded, described in part 330.

(10) Data and information about a prescription drug for human use submitted as part of the procedures for classifying these drugs as generally recognized as safe and effective and not misbranded, described in this chapter.

(11) [Reserved]

(12) An application for a biologics license, described in part 601 of this chapter.

(13) Data and information about a biological product submitted as part of the procedures for determining that licensed biological products are safe and effective and not misbranded, described in part 601.

(14) Data and information about an in vitro diagnostic product submitted as part of the procedures for establishing, amending, or repealing a standard for these products, described in part 809.

(15) An Application for an Investigational Device Exemption, described in part 812.

(16) Data and information about a medical device submitted as part of the procedures for classifying these devices, described in section 513.

(17) Data and information about a medical device submitted as part of the procedures for establishing, amending, or repealing a standard for these devices, described in section 514.

(18) An application for premarket approval of a medical device, described in section 515.

(19) A product development protocol for a medical device, described in section 515.

(20) Data and information about an electronic product submitted as part of the procedures for establishing, amending, or repealing a standard for these products, described in section 358 of the Public Health Service Act.

(21) Data and information about an electronic product submitted as part of the procedures for obtaining a variance from any electronic product performance standard, as described in §1010.4.

(22) Data and information about an electronic product submitted as part of the procedures for granting, amending, or extending an exemption from a radiation safety performance standard, as described in §1010.5.

(23) Data and information about a clinical study of an infant formula when submitted as part of an infant formula notification under section 412(c) of the Federal Food, Drug, and Cosmetic Act.

(24) Data and information submitted in a petition for a nutrient content claim, described in §101.69 of this chapter, or for a health claim, described in §101.70 of this chapter.

(25) Data and information from investigations involving children submitted in a new dietary ingredient notification, described in §190.6 of this chapter.

(c) Clinical investigation means any experiment that involves a test article and one or more human subjects and that either is subject to requirements for prior submission to the Food and Drug Administration under section 505(i) or 520(g) of the act, or is not
subject to requirements for prior submission to the Food and Drug Administration under these sections of the act, but the results of which are intended to be submitted later to, or held for inspection by, the Food and Drug Administration as part of an application for a research or marketing permit. The term does not include experiments that are subject to the provisions of part 58 of this chapter, regarding nonclinical laboratory studies.

(d) **Investigator** means an individual who actually conducts a clinical investigation, i.e., under whose immediate direction the test article is administered or dispensed to, or used involving, a subject, or, in the event of an investigation conducted by a team of individuals, is the responsible leader of that team.

(e) **Sponsor** means a person who initiates a clinical investigation, but who does not actually conduct the investigation, i.e., the test article is administered or dispensed to or used involving, a subject under the immediate direction of another individual. A person other than an individual (e.g., corporation or agency) that uses one or more of its own employees to conduct a clinical investigation it has initiated is considered to be a sponsor (not a sponsor-investigator), and the employees are considered to be investigators.

(f) **Sponsor-investigator** means an individual who both initiates and actually conducts, alone or with others, a clinical investigation, i.e., under whose immediate direction the test article is administered or dispensed to, or used involving, a subject. The term does not include any person other than an individual, e.g., corporation or agency.

(g) **Human subject** means an individual who is or becomes a participant in research, either as a recipient of the test article or as a control. A subject may be either a healthy human or a patient.

(h) **Institution** means any public or private entity or agency (including Federal, State, and other agencies). The word facility as used in section 520(g) of the act is deemed to be synonymous with the term institution for purposes of this part.

(i) **Institutional review board (IRB)** means any board, committee, or other group formally designated by an institution to review biomedical research involving humans as subjects, to approve the initiation of and conduct periodic review of such research. The term has the same meaning as the phrase institutional review committee as used in section 520(g) of the act.

(j) **Test article** means any drug (including a biological product for human use), medical device for human use, human food additive, color additive, electronic product, or any other article subject to regulation under the act or under sections 351 and 354-360F of the Public Health Service Act (42 U.S.C. 262 and 263b-263n).

(k) **Minimal risk** means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.

(l) **Legally authorized representative** means an individual or judicial or other body authorized under applicable law to consent on behalf of a prospective subject to the subject's participation in the procedure(s) involved in the research.

(m) **Family member** means any one of the following legally competent persons: Spouse; parents; children (including adopted children); brothers, sisters, and spouses of
brothers and sisters; and any individual related by blood or affinity whose close
association with the subject is the equivalent of a family relationship.

(n) **Assent** means a child's affirmative agreement to participate in a clinical investigation.
Mere failure to object may not, absent affirmative agreement, be construed as assent.

(o) **Children** means persons who have not attained the legal age for consent to treatments
or procedures involved in clinical investigations, under the applicable law of the
jurisdiction in which the clinical investigation will be conducted.

(p) **Parent** means a child's biological or adoptive parent.

(q) **Ward** means a child who is placed in the legal custody of the State or other agency,
institution, or entity, consistent with applicable Federal, State, or local law.

(r) **Permission** means the agreement of parent(s) or guardian to the participation of their
child or ward in a clinical investigation. Permission must be obtained in compliance
with subpart B of this part and must include the elements of informed consent
described in §50.25.

(s) **Guardian** means an individual who is authorized under applicable State or local law to
consent on behalf of a child to general medical care when general medical care
includes participation in research. For purposes of subpart D of this part, a guardian
also means an individual who is authorized to consent on behalf of a child to
participate in research.

**Subpart B--Informed Consent of Human Subjects**

§50.20 General requirements for informed consent.

*Source: 46 FR 8951, Jan. 27, 1981, unless otherwise noted.*

Except as provided in §§50.23 and 50.24, no investigator may involve a human being as a
subject in research covered by these regulations unless the investigator has obtained the
legally effective informed consent of the subject or the subject's legally authorized
representative. An investigator shall seek such consent only under circumstances that
provide the prospective subject or the representative sufficient opportunity to consider
whether or not to participate and that minimize the possibility of coercion or undue
influence. The information that is given to the subject or the representative shall be in
language understandable to the subject or the representative. No informed consent,
whether oral or written, may include any exculpatory language through which the subject
or the representative is made to waive or appear to waive any of the subject's legal rights,
or releases or appears to release the investigator, the sponsor, the institution, or its agents
from liability for negligence.

§50.23 Exception from general requirements.

(a) The obtaining of informed consent shall be deemed feasible unless, before use of the
test article (except as provided in paragraph (b) of this section), both the investigator
and a physician who is not otherwise participating in the clinical investigation certify
in writing all of the following:

(1) The human subject is confronted by a life-threatening situation necessitating the
use of the test article.

(2) Informed consent cannot be obtained from the subject because of an inability to
communicate with, or obtain legally effective consent from, the subject.
(3) Time is not sufficient to obtain consent from the subject's legal representative.
(4) There is available no alternative method of approved or generally recognized therapy that provides an equal or greater likelihood of saving the life of the subject.

(b) If immediate use of the test article is, in the investigator's opinion, required to preserve the life of the subject, and time is not sufficient to obtain the independent determination required in paragraph (a) of this section in advance of using the test article, the determinations of the clinical investigator shall be made and, within 5 working days after the use of the article, be reviewed and evaluated in writing by a physician who is not participating in the clinical investigation.

(c) The documentation required in paragraph (a) or (b) of this section shall be submitted to the IRB within 5 working days after the use of the test article.

(d) Under 10 U.S.C. 1107(f) the President may waive the prior consent requirement for the administration of an investigational new drug to a member of the armed forces in connection with the member's participation in a particular military operation. The statute specifies that only the President may waive informed consent in this connection and the President may grant such a waiver only if the President determines in writing that obtaining consent: Is not feasible; is contrary to the best interests of the military member; or is not in the interests of national security. The statute further provides that in making a determination to waive prior informed consent on the ground that it is not feasible or the ground that it is contrary to the best interests of the military members involved, the President shall apply the standards and criteria that are set forth in the relevant FDA regulations for a waiver of the prior informed consent requirements of section 505(i)(4) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(i)(4)). Before such a determination may be made that obtaining informed consent from military personnel prior to the use of an investigational drug (including an antibiotic or biological product) in a specific protocol under an investigational new drug application (IND) sponsored by the Department of Defense (DOD) and limited to specific military personnel involved in a particular military operation is not feasible or is contrary to the best interests of the military members involved the Secretary of Defense must first request such a determination from the President, and certify and document to the President that the following standards and criteria contained in paragraphs (d)(1) through (d)(4) of this section have been met.

(i) The extent and strength of evidence of the safety and effectiveness of the investigational new drug in relation to the medical risk that could be encountered during the military operation supports the drug's administration under an IND.

(ii) The military operation presents a substantial risk that military personnel may be subject to a chemical, biological, nuclear, or other exposure likely to produce death or serious or life-threatening injury or illness.

(iii) There is no available satisfactory alternative therapeutic or preventive treatment in relation to the intended use of the investigational new drug.
(iv) Conditioning use of the investigational new drug on the voluntary participation of each member could significantly risk the safety and health of any individual member who would decline its use, the safety of other military personnel, and the accomplishment of the military mission.

(v) A duly constituted institutional review board (IRB) established and operated in accordance with the requirements of paragraphs (d)(2) and (d)(3) of this section, responsible for review of the study, has reviewed and approved the investigational new drug protocol and the administration of the investigational new drug without informed consent. DOD's request is to include the documentation required by §56.115(a)(2) of this chapter.

(vi) DOD has explained:
   (A) The context in which the investigational drug will be administered, e.g., the setting or whether it will be self-administered or it will be administered by a health professional;
   (B) The nature of the disease or condition for which the preventive or therapeutic treatment is intended; and
   (C) To the extent there are existing data or information available, information on conditions that could alter the effects of the investigational drug.

(vii) DOD's recordkeeping system is capable of tracking and will be used to track the proposed treatment from supplier to the individual recipient.

(viii) Each member involved in the military operation will be given, prior to the administration of the investigational new drug, a specific written information sheet (including information required by 10 U.S.C. 1107(d)) concerning the investigational new drug, the risks and benefits of its use, potential side effects, and other pertinent information about the appropriate use of the product.

(ix) Medical records of members involved in the military operation will accurately document the receipt by members of the notification required by paragraph (d)(1)(viii) of this section.

(x) Medical records of members involved in the military operation will accurately document the receipt by members of any investigational new drugs in accordance with FDA regulations including part 312 of this chapter.

(xi) DOD will provide adequate followup to assess whether there are beneficial or adverse health consequences that result from the use of the investigational product.

(xii) DOD is pursuing drug development, including a time line, and marketing approval with due diligence.

(xiii) FDA has concluded that the investigational new drug protocol may proceed subject to a decision by the President on the informed consent waiver request.

(xiv) DOD will provide training to the appropriate medical personnel and potential recipients on the specific investigational new drug to be administered prior to its use.
(xv) DOD has stated and justified the time period for which the waiver is needed, not to exceed one year, unless separately renewed under these standards and criteria.

(xvi) DOD shall have a continuing obligation to report to the FDA and to the President any changed circumstances relating to these standards and criteria (including the time period referred to in paragraph (d)(1)(xv) of this section) or that otherwise might affect the determination to use an investigational new drug without informed consent.

(xvii) DOD is to provide public notice as soon as practicable and consistent with classification requirements through notice in the Federal Register describing each waiver of informed consent determination, a summary of the most updated scientific information on the products used, and other pertinent information.

(xviii) Use of the investigational drug without informed consent otherwise conforms with applicable law.

(2) The duly constituted institutional review board, described in paragraph (d)(1)(v) of this section, must include at least 3 nonaffiliated members who shall not be employees or officers of the Federal Government (other than for purposes of membership on the IRB) and shall be required to obtain any necessary security clearances. This IRB shall review the proposed IND protocol at a convened meeting at which a majority of the members are present including at least one member whose primary concerns are in nonscientific areas and, if feasible, including a majority of the nonaffiliated members. The information required by §56.115(a)(2) of this chapter is to be provided to the Secretary of Defense for further review.

(3) The duly constituted institutional review board, described in paragraph (d)(1)(v) of this section, must review and approve:

(i) The required information sheet;

(ii) The adequacy of the plan to disseminate information, including distribution of the information sheet to potential recipients, on the investigational product (e.g., in forms other than written);

(iii) The adequacy of the information and plans for its dissemination to health care providers, including potential side effects, contraindications, potential interactions, and other pertinent considerations; and

(iv) An informed consent form as required by part 50 of this chapter, in those circumstances in which DOD determines that informed consent may be obtained from some or all personnel involved.

(4) DOD is to submit to FDA summaries of institutional review board meetings at which the proposed protocol has been reviewed.

(5) Nothing in these criteria or standards is intended to preempt or limit FDA's and DOD's authority or obligations under applicable statutes and regulations.

Subpart B--Informed Consent of Human Subjects
§50.24 Exception from informed consent requirements for emergency research.

(a) The IRB responsible for the review, approval, and continuing review of the clinical investigation described in this section may approve that investigation without requiring that informed consent of all research subjects be obtained if the IRB (with the concurrence of a licensed physician who is a member of or consultant to the IRB and who is not otherwise participating in the clinical investigation) finds and documents each of the following:

1. The human subjects are in a life-threatening situation, available treatments are unproven or unsatisfactory, and the collection of valid scientific evidence, which may include evidence obtained through randomized placebo-controlled investigations, is necessary to determine the safety and effectiveness of particular interventions.

2. Obtaining informed consent is not feasible because:
   (i) The subjects will not be able to give their informed consent as a result of their medical condition;
   (ii) The intervention under investigation must be administered before consent from the subjects' legally authorized representatives is feasible; and
   (iii) There is no reasonable way to identify prospectively the individuals likely to become eligible for participation in the clinical investigation.

3. Participation in the research holds out the prospect of direct benefit to the subjects because:
   (i) Subjects are facing a life-threatening situation that necessitates intervention;
   (ii) Appropriate animal and other preclinical studies have been conducted, and the information derived from those studies and related evidence support the potential for the intervention to provide a direct benefit to the individual subjects; and
   (iii) Risks associated with the investigation are reasonable in relation to what is known about the medical condition of the potential class of subjects, the risks and benefits of standard therapy, if any, and what is known about the risks and benefits of the proposed intervention or activity.

4. The clinical investigation could not practicably be carried out without the waiver.

5. The proposed investigational plan defines the length of the potential therapeutic window based on scientific evidence, and the investigator has committed to attempting to contact a legally authorized representative for each subject within that window of time and, if feasible, to asking the legally authorized representative contacted for consent within that window rather than proceeding without consent. The investigator will summarize efforts made to contact legally authorized representatives and make this information available to the IRB at the time of continuing review.

6. The IRB has reviewed and approved informed consent procedures and an informed consent document consistent with §50.25. These procedures and the informed consent document are to be used with subjects or their legally authorized representatives in situations where use of such procedures and documents is feasible. The IRB has reviewed and approved procedures and information to be used when providing an opportunity for a family member to
object to a subject's participation in the clinical investigation consistent with paragraph (a)(7)(v) of this section.

(7) Additional protections of the rights and welfare of the subjects will be provided, including, at least:

(i) Consultation (including, where appropriate, consultation carried out by the IRB) with representatives of the communities in which the clinical investigation will be conducted and from which the subjects will be drawn;

(ii) Public disclosure to the communities in which the clinical investigation will be conducted and from which the subjects will be drawn, prior to initiation of the clinical investigation, of plans for the investigation and its risks and expected benefits;

(iii) Public disclosure of sufficient information following completion of the clinical investigation to apprise the community and researchers of the study, including the demographic characteristics of the research population, and its results;

(iv) Establishment of an independent data monitoring committee to exercise oversight of the clinical investigation; and

(v) If obtaining informed consent is not feasible and a legally authorized representative is not reasonably available, the investigator has committed, if feasible, to attempting to contact within the therapeutic window the subject's family member who is not a legally authorized representative, and asking whether he or she objects to the subject's participation in the clinical investigation. The investigator will summarize efforts made to contact family members and make this information available to the IRB at the time of continuing review.

(b) The IRB is responsible for ensuring that procedures are in place to inform, at the earliest feasible opportunity, each subject, or if the subject remains incapacitated, a legally authorized representative of the subject, or if such a representative is not reasonably available, a family member, of the subject's inclusion in the clinical investigation, the details of the investigation and other information contained in the informed consent document. The IRB shall also ensure that there is a procedure to inform the subject, or if the subject remains incapacitated, a legally authorized representative of the subject, or if such a representative is not reasonably available, a family member, that he or she may discontinue the subject's participation at any time without penalty or loss of benefits to which the subject is otherwise entitled. If a legally authorized representative or family member is told about the clinical investigation and the subject's condition improves, the subject is also to be informed as soon as feasible. If a subject is entered into a clinical investigation with waived consent and the subject dies before a legally authorized representative or family member can be contacted, information about the clinical investigation is to be provided to the subject's legally authorized representative or family member, if feasible.

(c) The IRB determinations required by paragraph (a) of this section and the documentation required by paragraph (e) of this section are to be retained by the IRB for at least 3 years after completion of the clinical investigation, and the records shall
be accessible for inspection and copying by FDA in accordance with §56.115(b) of this chapter.

(d) Protocols involving an exception to the informed consent requirement under this section must be performed under a separate investigational new drug application (IND) or investigational device exemption (IDE) that clearly identifies such protocols as protocols that may include subjects who are unable to consent. The submission of those protocols in a separate IND/IDE is required even if an IND for the same drug product or an IDE for the same device already exists. Applications for investigations under this section may not be submitted as amendments under §§312.30 or 812.35 of this chapter.

(e) If an IRB determines that it cannot approve a clinical investigation because the investigation does not meet the criteria in the exception provided under paragraph (a) of this section or because of other relevant ethical concerns, the IRB must document its findings and provide these findings promptly in writing to the clinical investigator and to the sponsor of the clinical investigation. The sponsor of the clinical investigation must promptly disclose this information to FDA and to the sponsor's clinical investigators who are participating or are asked to participate in this or a substantially equivalent clinical investigation of the sponsor, and to other IRB's that have been, or are, asked to review this or a substantially equivalent investigation by that sponsor.

§50.25 Elements of informed consent.

(a) Basic elements of informed consent. In seeking informed consent, the following information shall be provided to each subject:

(1) A statement that the study involves research, an explanation of the purposes of the research and the expected duration of the subject's participation, a description of the procedures to be followed, and identification of any procedures which are experimental.

(2) A description of any reasonably foreseeable risks or discomforts to the subject.

(3) A description of any benefits to the subject or to others which may reasonably be expected from the research.

(4) A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject.

(5) A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained and that notes the possibility that the Food and Drug Administration may inspect the records.

(6) For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained.

(7) An explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights, and whom to contact in the event of a research-related injury to the subject.

(8) A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and that
the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.

(b) Additional elements of informed consent. When appropriate, one or more of the following elements of information shall also be provided to each subject:

(1) A statement that the particular treatment or procedure may involve risks to the subject (or to the embryo or fetus, if the subject is or may become pregnant) which are currently unforeseeable.

(2) Anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's consent.

(3) Any additional costs to the subject that may result from participation in the research.

(4) The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject.

(5) A statement that significant new findings developed during the course of the research which may relate to the subject's willingness to continue participation will be provided to the subject.

(6) The approximate number of subjects involved in the study.

(c) The informed consent requirements in these regulations are not intended to preempt any applicable Federal, State, or local laws which require additional information to be disclosed for informed consent to be legally effective.

(d) Nothing in these regulations is intended to limit the authority of a physician to provide emergency medical care to the extent the physician is permitted to do so under applicable Federal, State, or local law.

§50.27 Documentation of informed consent.

(a) Except as provided in §56.109(c), informed consent shall be documented by the use of a written consent form approved by the IRB and signed and dated by the subject or the subject's legally authorized representative at the time of consent. A copy shall be given to the person signing the form.

(b) Except as provided in §56.109(c), the consent form may be either of the following:

(1) A written consent document that embodies the elements of informed consent required by §50.25. This form may be read to the subject or the subject's legally authorized representative, but, in any event, the investigator shall give either the subject or the representative adequate opportunity to read it before it is signed.

(2) A short form written consent document stating that the elements of informed consent required by §50.25 have been presented orally to the subject or the subject's legally authorized representative. When this method is used, there shall be a witness to the oral presentation. Also, the IRB shall approve a written summary of what is to be said to the subject or the representative. Only the short form itself is to be signed by the subject or the representative. However, the witness shall sign both the short form and a copy of the summary, and the person actually obtaining the consent shall sign a copy of the summary. A copy of the summary shall be given to the subject or the representative in addition to a copy of the short form. [46 FR 8951, Jan. 27, 1981, as amended at 61 FR 57280, Nov. 5, 1996]
Subpart C [Reserved]

Subpart D--Additional Safeguards for Children in Clinical Investigations

§50.50 IRB duties.
Source: 66 FR 20598, Apr. 24, 2001, unless otherwise noted.
In addition to other responsibilities assigned to IRBs under this part and part 56 of this chapter, each IRB must review clinical investigations involving children as subjects covered by this subpart D and approve only those clinical investigations that satisfy the criteria described in §50.51, §50.52, or §50.53 and the conditions of all other applicable sections of this subpart D.

§50.51 Clinical investigations not involving greater than minimal risk.
Any clinical investigation within the scope described in §§50.1 and 56.101 of this chapter in which no greater than minimal risk to children is presented may involve children as subjects only if the IRB finds and documents that adequate provisions are made for soliciting the assent of the children and the permission of their parents or guardians as set forth in §50.55.

§50.52 Clinical investigations involving greater than minimal risk but presenting the prospect of direct benefit to individual subjects.
Any clinical investigation within the scope described in §§50.1 and 56.101 of this chapter in which more than minimal risk to children is presented by an intervention or procedure that holds out the prospect of direct benefit for the individual subject, or by a monitoring procedure that is likely to contribute to the subject's well-being, may involve children as subjects only if the IRB finds and documents that:
(a) The risk is justified by the anticipated benefit to the subjects;
(b) The relation of the anticipated benefit to the risk is at least as favorable to the subjects as that presented by available alternative approaches; and
(c) Adequate provisions are made for soliciting the assent of the children and permission of their parents or guardians as set forth in §50.55.

§50.53 Clinical investigations involving greater than minimal risk and no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subjects' disorder or condition.
Any clinical investigation within the scope described in §§50.1 and 56.101 of this chapter in which more than minimal risk to children is presented by an intervention or procedure that does not hold out the prospect of direct benefit for the individual subject, or by a monitoring procedure that is not likely to contribute to the well-being of the subject, may involve children as subjects only if the IRB finds and documents that:
(a) The risk represents a minor increase over minimal risk;
(b) The intervention or procedure presents experiences to subjects that are reasonably commensurate with those inherent in their actual or expected medical, dental, psychological, social, or educational situations;
(c) The intervention or procedure is likely to yield generalizable knowledge about the subjects' disorder or condition that is of vital importance for the understanding or amelioration of the subjects' disorder or condition; and
(d) Adequate provisions are made for soliciting the assent of the children and permission of their parents or guardians as set forth in §50.55.

§50.54 Clinical investigations not otherwise approvable that present an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children.

If an IRB does not believe that a clinical investigation within the scope described in §§50.1 and 56.101 of this chapter and involving children as subjects meets the requirements of §50.51, §50.52, or §50.53, the clinical investigation may proceed only if:

(a) The IRB finds and documents that the clinical investigation presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children; and
(b) The Commissioner of Food and Drugs, after consultation with a panel of experts in pertinent disciplines (for example: science, medicine, education, ethics, law) and following opportunity for public review and comment, determines either:
(1) That the clinical investigation in fact satisfies the conditions of §50.51, §50.52, or §50.53, as applicable, or
(2) That the following conditions are met:
(i) The clinical investigation presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children;
(ii) The clinical investigation will be conducted in accordance with sound ethical principles; and
(iii) Adequate provisions are made for soliciting the assent of children and the permission of their parents or guardians as set forth in §50.55.

§50.55 Requirements for permission by parents or guardians and for assent by children.

(a) In addition to the determinations required under other applicable sections of this subpart D, the IRB must determine that adequate provisions are made for soliciting the assent of the children when in the judgment of the IRB the children are capable of providing assent.
(b) In determining whether children are capable of providing assent, the IRB must take into account the ages, maturity, and psychological state of the children involved. This judgment may be made for all children to be involved in clinical investigations under a particular protocol, or for each child, as the IRB deems appropriate.
(c) The assent of the children is not a necessary condition for proceeding with the clinical investigation if the IRB determines:
(1) That the capability of some or all of the children is so limited that they cannot reasonably be consulted, or
(2) That the intervention or procedure involved in the clinical investigation holds out a prospect of direct benefit that is important to the health or well-being of the children and is available only in the context of the clinical investigation.
(d) Even where the IRB determines that the subjects are capable of assenting, the IRB may still waive the assent requirement if it finds and documents that:
   (1) The clinical investigation involves no more than minimal risk to the subjects;
   (2) The waiver will not adversely affect the rights and welfare of the subjects;
   (3) The clinical investigation could not practicably be carried out without the waiver; and
   (4) Whenever appropriate, the subjects will be provided with additional pertinent information after participation.

(e) In addition to the determinations required under other applicable sections of this subpart D, the IRB must determine that the permission of each child's parents or guardian is granted.
   (1) Where parental permission is to be obtained, the IRB may find that the permission of one parent is sufficient, if consistent with State law, for clinical investigations to be conducted under §50.51 or §50.52.
   (2) Where clinical investigations are covered by §50.53 or §50.54 and permission is to be obtained from parents, both parents must give their permission unless one parent is deceased, unknown, incompetent, or not reasonably available, or when only one parent has legal responsibility for the care and custody of the child if consistent with State law.

(f) Permission by parents or guardians must be documented in accordance with and to the extent required by §50.27.

(g) When the IRB determines that assent is required, it must also determine whether and how assent must be documented.

§50.56 Wards.

(a) Children who are wards of the State or any other agency, institution, or entity can be included in clinical investigations approved under §50.53 or §50.54 only if such clinical investigations are:
   (1) Related to their status as wards; or
   (2) Conducted in schools, camps, hospitals, institutions, or similar settings in which the majority of children involved as subjects are not wards.

(b) If the clinical investigation is approved under paragraph (a) of this section, the IRB must require appointment of an advocate for each child who is a ward.
   (1) The advocate will serve in addition to any other individual acting on behalf of the child as guardian or in loco parentis.
   (2) One individual may serve as advocate for more than one child.
   (3) The advocate must be an individual who has the background and experience to act in, and agrees to act in, the best interest of the child for the duration of the child's participation in the clinical investigation.
   (4) The advocate must not be associated in any way (except in the role as advocate or member of the IRB) with the clinical investigation, the investigator(s), or the guardian organization.
§54.1 Purpose.
(a) The Food and Drug Administration (FDA) evaluates clinical studies submitted in marketing applications, required by law, for new human drugs and biological products and marketing applications and reclassification petitions for medical devices.
(b) The agency reviews data generated in these clinical studies to determine whether the applications are approvable under the statutory requirements. FDA may consider clinical studies inadequate and the data inadequate if, among other things, appropriate steps have not been taken in the design, conduct, reporting, and analysis of the studies to minimize bias. One potential source of bias in clinical studies is a financial interest of the clinical investigator in the outcome of the study because of the way payment is arranged (e.g., a royalty) or because the investigator has a proprietary interest in the product (e.g., a patent) or because the investigator has an equity interest in the sponsor of the covered study. This section and conforming regulations require an applicant whose submission relies in part on clinical data to disclose certain financial arrangements between sponsor(s) of the covered studies and the clinical investigators and certain interests of the clinical investigators in the product under study or in the sponsor of the covered studies. FDA will use this information, in conjunction with information about the design and purpose of the study, as well as information obtained through on-site inspections, in the agency’s assessment of the reliability of the data.

§54.2 Definitions.
For the purposes of this part:
(a) Compensation affected by the outcome of clinical studies means compensation that could be higher for a favorable outcome than for an unfavorable outcome, such as compensation that is explicitly greater for a favorable result or compensation to the investigator in the form of an equity interest in the sponsor of a covered study or in the form of compensation tied to sales of the product, such as a royalty interest.
(b) Significant equity interest in the sponsor of a covered study means any ownership interest, stock options, or other financial interest whose value cannot be readily determined through reference to public prices (generally, interests in a nonpublicly traded corporation), or any equity interest in a publicly traded corporation that exceeds $50,000 during the time the clinical investigator is carrying out the study and for 1 year following completion of the study.
(c) Proprietary interest in the tested product means property or other financial interest in the product including, but not limited to, a patent, trademark, copyright or licensing agreement.
(d) Clinical investigator means only a listed or identified investigator or subinvestigator who is directly involved in the treatment or evaluation of research subjects. The term also includes the spouse and each dependent child of the investigator.
(e) *Covered clinical study* means any study of a drug or device in humans submitted in a marketing application or reclassification petition subject to this part that the applicant or FDA relies on to establish that the product is effective (including studies that show equivalence to an effective product) or any study in which a single investigator makes a significant contribution to the demonstration of safety. This would, in general, not include phase I tolerance studies or pharmacokinetic studies, most clinical pharmacology studies (unless they are critical to an efficacy determination), large open safety studies conducted at multiple sites, treatment protocols, and parallel track protocols. An applicant may consult with FDA as to which clinical studies constitute “covered clinical studies” for purposes of complying with financial disclosure requirements.

(f) *Significant payments of other sorts* means payments made by the sponsor of a covered study to the investigator or the institution to support activities of the investigator that have a monetary value of more than $25,000, exclusive of the costs of conducting the clinical study or other clinical studies, (e.g., a grant to fund ongoing research, compensation in the form of equipment or retainers for ongoing consultation or honoraria) during the time the clinical investigator is carrying out the study and for 1 year following the completion of the study.

(g) *Applicant* means the party who submits a marketing application to FDA for approval of a drug, device, or biologic product. The applicant is responsible for submitting the appropriate certification and disclosure statements required in this part.

(h) *Sponsor of the covered clinical study* means the party supporting a particular study at the time it was carried out.


§54.3 Scope.

The requirements in this part apply to any applicant who submits a marketing application for a human drug, biological product, or device and who submits covered clinical studies. The applicant is responsible for making the appropriate certification or disclosure statement where the applicant either contracted with one or more clinical investigators to conduct the studies or submitted studies conducted by others not under contract to the applicant.

§54.4 Certification and disclosure requirements.

For purposes of this part, an applicant must submit a list of all clinical investigators who conducted covered clinical studies to determine whether the applicant's product meets FDA's marketing requirements, identifying those clinical investigators who are full-time or part-time employees of the sponsor of each covered study. The applicant must also completely and accurately disclose or certify information concerning the financial interests of a clinical investigator who is not a full-time or part-time employee of the sponsor for each covered clinical study. Clinical investigators subject to investigational new drug or investigational device exemption regulations must provide the sponsor of the study with sufficient accurate information needed to allow subsequent disclosure or certification. The applicant is required to submit for each clinical investigator who participates in a covered study, either a certification that none of the financial
arrangements described in §54.2 exist, or disclose the nature of those arrangements to the agency. Where the applicant acts with due diligence to obtain the information required in this section but is unable to do so, the applicant shall certify that despite the applicant's due diligence in attempting to obtain the information, the applicant was unable to obtain the information and shall include the reason.

(a) The applicant (of an application submitted under sections 505, 506, 510(k), 513, or 515 of the Federal Food, Drug, and Cosmetic Act, or section 351 of the Public Health Service Act) that relies in whole or in part on clinical studies shall submit, for each clinical investigator who participated in a covered clinical study, either a certification described in paragraph (a)(1) of this section or a disclosure statement described in paragraph (a)(3) of this section.

(1) Certification: The applicant covered by this section shall submit for all clinical investigators (as defined in §54.2(d)), to whom the certification applies, a completed Form FDA 3454 attesting to the absence of financial interests and arrangements described in paragraph (a)(3) of this section. The form shall be dated and signed by the chief financial officer or other responsible corporate official or representative.

(2) If the certification covers less than all covered clinical data in the application, the applicant shall include in the certification a list of the studies covered by this certification.

(3) Disclosure Statement: For any clinical investigator defined in §54.2(d) for whom the applicant does not submit the certification described in paragraph (a)(1) of this section, the applicant shall submit a completed Form FDA 3455 disclosing completely and accurately the following:

(i) Any financial arrangement entered into between the sponsor of the covered study and the clinical investigator involved in the conduct of a covered clinical trial, whereby the value of the compensation to the clinical investigator for conducting the study could be influenced by the outcome of the study;

(ii) Any significant payments of other sorts from the sponsor of the covered study, such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation, or honoraria;

(iii) Any proprietary interest in the tested product held by any clinical investigator involved in a study;

(iv) Any significant equity interest in the sponsor of the covered study held by any clinical investigator involved in any clinical study; and

(v) Any steps taken to minimize the potential for bias resulting from any of the disclosed arrangements, interests, or payments.

(b) The clinical investigator shall provide to the sponsor of the covered study sufficient accurate financial information to allow the sponsor to submit complete and accurate certification or disclosure statements as required in paragraph (a) of this section. The investigator shall promptly update this information if any relevant changes occur in the course of the investigation or for 1 year following completion of the study.

(c) Refusal to file application. FDA may refuse to file any marketing application described in paragraph (a) of this section that does not contain the information required by this section or a certification by the applicant that the applicant has acted
with due diligence to obtain the information but was unable to do so and stating the reason.


§54.5 Agency evaluation of financial interests.
(a) Evaluation of disclosure statement. FDA will evaluate the information disclosed under §54.4(a)(2) about each covered clinical study in an application to determine the impact of any disclosed financial interests on the reliability of the study. FDA may consider both the size and nature of a disclosed financial interest (including the potential increase in the value of the interest if the product is approved) and steps that have been taken to minimize the potential for bias.
(b) Effect of study design. In assessing the potential of an investigator's financial interests to bias a study, FDA will take into account the design and purpose of the study. Study designs that utilize such approaches as multiple investigators (most of whom do not have a disclosable interest), blinding, objective endpoints, or measurement of endpoints by someone other than the investigator may adequately protect against any bias created by a disclosable financial interest.
(c) Agency actions to ensure reliability of data. If FDA determines that the financial interests of any clinical investigator raise a serious question about the integrity of the data, FDA will take any action it deems necessary to ensure the reliability of the data including:
   (1) Initiating agency audits of the data derived from the clinical investigator in question;
   (2) Requesting that the applicant submit further analyses of data, e.g., to evaluate the effect of the clinical investigator's data on overall study outcome;
   (3) Requesting that the applicant conduct additional independent studies to confirm the results of the questioned study; and
   (4) Refusing to treat the covered clinical study as providing data that can be the basis for an agency action.

§54.6 Recordkeeping and record retention.
(a) Financial records of clinical investigators to be retained. An applicant who has submitted a marketing application containing covered clinical studies shall keep on file certain information pertaining to the financial interests of clinical investigators who conducted studies on which the application relies and who are not full or part-time employees of the applicant, as follows:
   (1) Complete records showing any financial interest or arrangement as described in §54.4(a)(3)(i) paid to such clinical investigators by the sponsor of the covered study.
   (2) Complete records showing significant payments of other sorts, as described in §54.4(a)(3)(ii), made by the sponsor of the covered clinical study to the clinical investigator.
   (3) Complete records showing any financial interests held by clinical investigators as set forth in §54.4(a)(3)(iii) and (a)(3)(iv).
(b) Requirements for maintenance of clinical investigators' financial records.
(1) For any application submitted for a covered product, an applicant shall retain records as described in paragraph (a) of this section for 2 years after the date of approval of the application.

(2) The person maintaining these records shall, upon request from any properly authorized officer or employee of FDA, at reasonable times, permit such officer or employee to have access to and copy and verify these records.
Subpart A--General Provisions

§56.101 Scope.
(a) This part contains the general standards for the composition, operation, and responsibility of an Institutional Review Board (IRB) that reviews clinical investigations regulated by the Food and Drug Administration under sections 505(i) and 520(g) of the act, as well as clinical investigations that support applications for research or marketing permits for products regulated by the Food and Drug Administration, including foods, including dietary supplements, that bear a nutrient content claim or a health claim, infant formulas, food and color additives, drugs for human use, medical devices for human use, biological products for human use, and electronic products. Compliance with this part is intended to protect the rights and welfare of human subjects involved in such investigations.
(b) References in this part to regulatory sections of the Code of Federal Regulations are to chapter I of title 21, unless otherwise noted.

§56.102 Definitions.
As used in this part:
(b) Application for research or marketing permit includes:
(1) A color additive petition, described in part 71.
(2) Data and information regarding a substance submitted as part of the procedures for establishing that a substance is generally recognized as safe for a use which results or may reasonably be expected to result, directly or indirectly, in its becoming a component or otherwise affecting the characteristics of any food, described in §170.35.
(3) A food additive petition, described in part 171.
(4) Data and information regarding a food additive submitted as part of the procedures regarding food additives permitted to be used on an interim basis pending additional study, described in §180.1.
(5) Data and information regarding a substance submitted as part of the procedures for establishing a tolerance for unavoidable contaminants in food and food-packaging materials, described in section 406 of the act.
(6) An investigational new drug application, described in part 312 of this chapter.
(7) A new drug application, described in part 314.
(8) Data and information regarding the bioavailability or bioequivalence of drugs for human use submitted as part of the procedures for issuing, amending, or repealing a bioequivalence requirement, described in part 320.
(9) Data and information regarding an over-the-counter drug for human use submitted as part of the procedures for classifying such drugs as generally recognized as safe and effective and not misbranded, described in part 330.

(10) An application for a biologics license, described in part 601 of this chapter.

(11) Data and information regarding a biological product submitted as part of the procedures for determining that licensed biological products are safe and effective and not misbranded, as described in part 601 of this chapter.

(12) An Application for an Investigational Device Exemption, described in parts 812 and 813.

(13) Data and information regarding a medical device for human use submitted as part of the procedures for classifying such devices, described in part 860.

(14) Data and information regarding a medical device for human use submitted as part of the procedures for establishing, amending, or repealing a standard for such device, described in part 861.

(15) An application for premarket approval of a medical device for human use, described in section 515 of the act.

(16) A product development protocol for a medical device for human use, described in section 515 of the act.

(17) Data and information regarding an electronic product submitted as part of the procedures for establishing, amending, or repealing a standard for such products, described in section 358 of the Public Health Service Act.

(18) Data and information regarding an electronic product submitted as part of the procedures for obtaining a variance from any electronic product performance standard, as described in §1010.4.

(19) Data and information regarding an electronic product submitted as part of the procedures for granting, amending, or extending an exemption from a radiation safety performance standard, as described in §1010.5.

(20) Data and information regarding an electronic product submitted as part of the procedures for obtaining an exemption from notification of a radiation safety defect or failure of compliance with a radiation safety performance standard, described in subpart D of part 1003.

(21) Data and information about a clinical study of an infant formula when submitted as part of an infant formula notification under section 412(c) of the Federal Food, Drug, and Cosmetic Act.

(22) Data and information submitted in a petition for a nutrient content claim, described in §101.69 of this chapter, and for a health claim, described in §101.70 of this chapter.

(23) Data and information from investigations involving children submitted in a new dietary ingredient notification, described in §190.6 of this chapter.

(c) Clinical investigation means any experiment that involves a test article and one or more human subjects, and that either must meet the requirements for prior submission to the Food and Drug Administration under section 505(i) or 520(g) of the act, or need not meet the requirements for prior submission to the Food and Drug Administration under these sections of the act, but the results of which are intended to be later submitted to, or held for inspection by, the Food and Drug Administration as part of an application for a research or marketing permit. The term does not include
experiments that must meet the provisions of part 58, regarding nonclinical laboratory studies. The terms research, clinical research, clinical study, study, and clinical investigation are deemed to be synonymous for purposes of this part.

(d) Emergency use means the use of a test article on a human subject in a life-threatening situation in which no standard acceptable treatment is available, and in which there is not sufficient time to obtain IRB approval.

(e) Human subject means an individual who is or becomes a participant in research, either as a recipient of the test article or as a control. A subject may be either a healthy individual or a patient.

(f) Institution means any public or private entity or agency (including Federal, State, and other agencies). The term facility as used in section 520(g) of the act is deemed to be synonymous with the term institution for purposes of this part.

(g) Institutional Review Board (IRB) means any board, committee, or other group formally designated by an institution to review, to approve the initiation of, and to conduct periodic review of, biomedical research involving human subjects. The primary purpose of such review is to assure the protection of the rights and welfare of the human subjects. The term has the same meaning as the phrase institutional review committee as used in section 520(g) of the act.

(h) Investigator means an individual who actually conducts a clinical investigation (i.e., under whose immediate direction the test article is administered or dispensed to, or used involving, a subject) or, in the event of an investigation conducted by a team of individuals, is the responsible leader of that team.

(i) Minimal risk means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.

(j) Sponsor means a person or other entity that initiates a clinical investigation, but that does not actually conduct the investigation, i.e., the test article is administered or dispensed to, or used involving, a subject under the immediate direction of another individual. A person other than an individual (e.g., a corporation or agency) that uses one or more of its own employees to conduct an investigation that it has initiated is considered to be a sponsor (not a sponsor-investigator), and the employees are considered to be investigators.

(k) Sponsor-investigator means an individual who both initiates and actually conducts, alone or with others, a clinical investigation, i.e., under whose immediate direction the test article is administered or dispensed to, or used involving, a subject. The term does not include any person other than an individual, e.g., it does not include a corporation or agency. The obligations of a sponsor-investigator under this part include both those of a sponsor and those of an investigator.

(l) Test article means any drug for human use, biological product for human use, medical device for human use, human food additive, color additive, electronic product, or any other article subject to regulation under the act or under sections 351 or 354-360F of the Public Health Service Act.

(m) IRB approval means the determination of the IRB that the clinical investigation has been reviewed and may be conducted at an institution within the constraints set forth by the IRB and by other institutional and Federal requirements.
§56.103 Circumstances in which IRB review is required.

(a) Except as provided in §§56.104 and 56.105, any clinical investigation which must meet the requirements for prior submission (as required in parts 312, 812, and 813) to the Food and Drug Administration shall not be initiated unless that investigation has been reviewed and approved by, and remains subject to continuing review by, an IRB meeting the requirements of this part.

(b) Except as provided in §§56.104 and 56.105, the Food and Drug Administration may decide not to consider in support of an application for a research or marketing permit any data or information that has been derived from a clinical investigation that has not been approved by, and that was not subject to initial and continuing review by, an IRB meeting the requirements of this part. The determination that a clinical investigation may not be considered in support of an application for a research or marketing permit does not, however, relieve the applicant for such a permit of any obligation under any other applicable regulations to submit the results of the investigation to the Food and Drug Administration.

(c) Compliance with these regulations will in no way render inapplicable pertinent Federal, State, or local laws or regulations.

§56.104 Exemptions from IRB requirement.

The following categories of clinical investigations are exempt from the requirements of this part for IRB review:

(a) Any investigation which commenced before July 27, 1981 and was subject to requirements for IRB review under FDA regulations before that date, provided that the investigation remains subject to review of an IRB which meets the FDA requirements in effect before July 27, 1981.

(b) Any investigation commenced before July 27, 1981 and was not otherwise subject to requirements for IRB review under Food and Drug Administration regulations before that date.

(c) Emergency use of a test article, provided that such emergency use is reported to the IRB within 5 working days. Any subsequent use of the test article at the institution is subject to IRB review.

(d) Taste and food quality evaluations and consumer acceptance studies, if wholesome foods without additives are consumed or if a food is consumed that contains a food ingredient at or below the level and for a use found to be safe, or agricultural, chemical, or environmental contaminant at or below the level found to be safe, by the Food and Drug Administration or approved by the Environmental Protection Agency or the Food Safety and Inspection Service of the U.S. Department of Agriculture.

§56.105 Waiver of IRB requirement.

On the application of a sponsor or sponsor-investigator, the Food and Drug Administration may waive any of the requirements contained in these regulations, including the requirements for IRB review, for specific research activities or for classes of research activities, otherwise covered by these regulations. 21 CFR 56.107
Subpart B--Organization and Personnel

§56.107 IRB membership.
(a) Each IRB shall have at least five members, with varying backgrounds to promote complete and adequate review of research activities commonly conducted by the institution. The IRB shall be sufficiently qualified through the experience and expertise of its members, and the diversity of the members, including consideration of race, gender, cultural backgrounds, and sensitivity to such issues as community attitudes, to promote respect for its advice and counsel in safeguarding the rights and welfare of human subjects. In addition to possessing the professional competence necessary to review the specific research activities, the IRB shall be able to ascertain the acceptability of proposed research in terms of institutional commitments and regulations, applicable law, and standards or professional conduct and practice. The IRB shall therefore include persons knowledgeable in these areas. If an IRB regularly reviews research that involves a vulnerable category of subjects, such as children, prisoners, pregnant women, or handicapped or mentally disabled persons, consideration shall be given to the inclusion of one or more individuals who are knowledgeable about and experienced in working with those subjects.
(b) Every nondiscriminatory effort will be made to ensure that no IRB consists entirely of men or entirely of women, including the institution's consideration of qualified persons of both sexes, so long as no selection is made to the IRB on the basis of gender. No IRB may consist entirely of members of one profession.
(c) Each IRB shall include at least one member whose primary concerns are in the scientific area and at least one member whose primary concerns are in nonscientific areas.
(d) Each IRB shall include at least one member who is not otherwise affiliated with the institution and who is not part of the immediate family of a person who is affiliated with the institution.
(e) No IRB may have a member participate in the IRB's initial or continuing review of any project in which the member has a conflicting interest, except to provide information requested by the IRB.
(f) An IRB may, in its discretion, invite individuals with competence in special areas to assist in the review of complex issues which require expertise beyond or in addition to that available on the IRB. These individuals may not vote with the IRB.

Subpart C--IRB Functions and Operations

§56.108 IRB functions and operations.
In order to fulfill the requirements of these regulations, each IRB shall:
(a) Follow written procedures:
   (1) For conducting its initial and continuing review of research and for reporting its findings and actions to the investigator and the institution;
   (2) for determining which projects require review more often than annually and which projects need verification from sources other than the investigator that no material changes have occurred since previous IRB review;
(3) for ensuring prompt reporting to the IRB of changes in research activity; and
(4) for ensuring that changes in approved research, during the period for which IRB approval has already been given, may not be initiated without IRB review and approval except where necessary to eliminate apparent immediate hazards to the human subjects.

(b) Follow written procedures for ensuring prompt reporting to the IRB, appropriate institutional officials, and the Food and Drug Administration of:
   (1) Any unanticipated problems involving risks to human subjects or others;
   (2) any instance of serious or continuing noncompliance with these regulations or the requirements or determinations of the IRB; or
   (3) any suspension or termination of IRB approval.

(c) Except when an expedited review procedure is used (see §56.110), review proposed research at convened meetings at which a majority of the members of the IRB are present, including at least one member whose primary concerns are in nonscientific areas. In order for the research to be approved, it shall receive the approval of a majority of those members present at the meeting.

§56.109 IRB review of research.

(a) An IRB shall review and have authority to approve, require modifications in (to secure approval), or disapprove all research activities covered by these regulations.

(b) An IRB shall require that information given to subjects as part of informed consent is in accordance with §50.25. The IRB may require that information, in addition to that specifically mentioned in §50.25, be given to the subjects when in the IRB’s judgment the information would meaningfully add to the protection of the rights and welfare of subjects.

(c) An IRB shall require documentation of informed consent in accordance with §50.27 of this chapter, except as follows:
   (1) The IRB may, for some or all subjects, waive the requirement that the subject, or the subject's legally authorized representative, sign a written consent form if it finds that the research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside the research context; or
   (2) The IRB may, for some or all subjects, find that the requirements in §50.24 of this chapter for an exception from informed consent for emergency research are met.

(d) In cases where the documentation requirement is waived under paragraph (c)(1) of this section, the IRB may require the investigator to provide subjects with a written statement regarding the research.

(e) An IRB shall notify investigators and the institution in writing of its decision to approve or disapprove the proposed research activity, or of modifications required to secure IRB approval of the research activity. If the IRB decides to disapprove a research activity, it shall include in its written notification a statement of the reasons for its decision and give the investigator an opportunity to respond in person or in writing. For investigations involving an exception to informed consent under §50.24 of this chapter, an IRB shall promptly notify in writing the investigator and the sponsor of the research when an IRB determines that it cannot approve the research because it does not meet the criteria in the exception provided under §50.24(a) of this chapter.
chapter or because of other relevant ethical concerns. The written notification shall include a statement of the reasons for the IRB's determination.

(f) An IRB shall conduct continuing review of research covered by these regulations at intervals appropriate to the degree of risk, but not less than once per year, and shall have authority to observe or have a third party observe the consent process and the research.

(g) An IRB shall provide in writing to the sponsor of research involving an exception to informed consent under §50.24 of this chapter a copy of information that has been publicly disclosed under §50.24(a)(7)(ii) and (a)(7)(iii) of this chapter. The IRB shall provide this information to the sponsor promptly so that the sponsor is aware that such disclosure has occurred. Upon receipt, the sponsor shall provide copies of the information disclosed to FDA.

(h) When some or all of the subjects in a study are children, an IRB must determine that the research study is in compliance with part 50, subpart D of this chapter, at the time of its initial review of the research. When some or all of the subjects in a study that is ongoing on April 30, 2001 are children, an IRB must conduct a review of the research to determine compliance with part 50, subpart D of this chapter, either at the time of continuing review or, at the discretion of the IRB, at an earlier date.

§56.110 Expedited review procedures for certain kinds of research involving no more than minimal risk, and for minor changes in approved research.

(a) The Food and Drug Administration has established, and published in the Federal Register, a list of categories of research that may be reviewed by the IRB through an expedited review procedure. The list will be amended, as appropriate, through periodic republication in the Federal Register.

(b) An IRB may use the expedited review procedure to review either or both of the following:

1. Some or all of the research appearing on the list and found by the reviewer(s) to involve no more than minimal risk,
2. minor changes in previously approved research during the period (of 1 year or less) for which approval is authorized.

Under an expedited review procedure, the review may be carried out by the IRB chairperson or by one or more experienced reviewers designated by the IRB chairperson from among the members of the IRB. In reviewing the research, the reviewers may exercise all of the authorities of the IRB except that the reviewers may not disapprove the research. A research activity may be disapproved only after review in accordance with the nonexpedited review procedure set forth in §56.108(c).

(c) Each IRB which uses an expedited review procedure shall adopt a method for keeping all members advised of research proposals which have been approved under the procedure.

(d) The Food and Drug Administration may restrict, suspend, or terminate an institution's or IRB's use of the expedited review procedure when necessary to protect the rights or welfare of subjects.
§56.111 Criteria for IRB approval of research.

(a) In order to approve research covered by these regulations the IRB shall determine that all of the following requirements are satisfied:

(1) Risks to subjects are minimized:
   (i) By using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk, and
   (ii) whenever appropriate, by using procedures already being performed on the subjects for diagnostic or treatment purposes.

(2) Risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may be expected to result. In evaluating risks and benefits, the IRB should consider only those risks and benefits that may result from the research (as distinguished from risks and benefits of therapies that subjects would receive even if not participating in the research). The IRB should not consider possible long-range effects of applying knowledge gained in the research (for example, the possible effects of the research on public policy) as among those research risks that fall within the purview of its responsibility.

(3) Selection of subjects is equitable. In making this assessment the IRB should take into account the purposes of the research and the setting in which the research will be conducted and should be particularly cognizant of the special problems of research involving vulnerable populations, such as children, prisoners, pregnant women, handicapped, or mentally disabled persons, or economically or educationally disadvantaged persons.

(4) Informed consent will be sought from each prospective subject or the subject's legally authorized representative, in accordance with and to the extent required by part 50.

(5) Informed consent will be appropriately documented, in accordance with and to the extent required by §50.27.

(6) Where appropriate, the research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects.

(7) Where appropriate, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data.

(b) When some or all of the subjects, such as children, prisoners, pregnant women, handicapped, or mentally disabled persons, or economically or educationally disadvantaged persons, are likely to be vulnerable to coercion or undue influence additional safeguards have been included in the study to protect the rights and welfare of these subjects.

(c) In order to approve research in which some or all of the subjects are children, an IRB must determine that all research is in compliance with part 50, subpart D of this chapter.

§56.112 Review by institution.

Research covered by these regulations that has been approved by an IRB may be subject to further appropriate review and approval or disapproval by officials of the institution. However, those officials may not approve the research if it has not been approved by an IRB.
§56.113 Suspension or termination of IRB approval of research.
An IRB shall have authority to suspend or terminate approval of research that is not being conducted in accordance with the IRB's requirements or that has been associated with unexpected serious harm to subjects. Any suspension or termination of approval shall include a statement of the reasons for the IRB's action and shall be reported promptly to the investigator, appropriate institutional officials, and the Food and Drug Administration.

§56.114 Cooperative research.
In complying with these regulations, institutions involved in multi-institutional studies may use joint review, reliance upon the review of another qualified IRB, or similar arrangements aimed at avoidance of duplication of effort.

Subpart D--Records and Reports

§56.115 IRB records.
(a) An institution, or where appropriate an IRB, shall prepare and maintain adequate documentation of IRB activities, including the following:
   (1) Copies of all research proposals reviewed, scientific evaluations, if any, that accompany the proposals, approved sample consent documents, progress reports submitted by investigators, and reports of injuries to subjects.
   (2) Minutes of IRB meetings which shall be in sufficient detail to show attendance at the meetings; actions taken by the IRB; the vote on these actions including the number of members voting for, against, and abstaining; the basis for requiring changes in or disapproving research; and a written summary of the discussion of controverted issues and their resolution.
   (3) Records of continuing review activities.
   (4) Copies of all correspondence between the IRB and the investigators.
   (5) A list of IRB members identified by name; earned degrees; representative capacity; indications of experience such as board certifications, licenses, etc., sufficient to describe each member's chief anticipated contributions to IRB deliberations; and any employment or other relationship between each member and the institution; for example: full-time employee, part-time employee, a member of governing panel or board, stockholder, paid or unpaid consultant.
   (6) Written procedures for the IRB as required by §56.108 (a) and (b).
   (7) Statements of significant new findings provided to subjects, as required by §50.25.
(b) The records required by this regulation shall be retained for at least 3 years after completion of the research, and the records shall be accessible for inspection and copying by authorized representatives of the Food and Drug Administration at reasonable times and in a reasonable manner.
(c) The Food and Drug Administration may refuse to consider a clinical investigation in support of an application for a research or marketing permit if the institution or the IRB that reviewed the investigation refuses to allow an inspection under this section.
Subpart E--Administrative Actions for Noncompliance

§56.120 Lesser administrative actions.
(a) If apparent noncompliance with these regulations in the operation of an IRB is observed by an FDA investigator during an inspection, the inspector will present an oral or written summary of observations to an appropriate representative of the IRB. The Food and Drug Administration may subsequently send a letter describing the noncompliance to the IRB and to the parent institution. The agency will require that the IRB or the parent institution respond to this letter within a time period specified by FDA and describe the corrective actions that will be taken by the IRB, the institution, or both to achieve compliance with these regulations.
(b) On the basis of the IRB's or the institution's response, FDA may schedule a reinspection to confirm the adequacy of corrective actions. In addition, until the IRB or the parent institution takes appropriate corrective action, the agency may:
(1) Withhold approval of new studies subject to the requirements of this part that are conducted at the institution or reviewed by the IRB;
(2) Direct that no new subjects be added to ongoing studies subject to this part;
(3) Terminate ongoing studies subject to this part when doing so would not endanger the subjects; or
(4) When the apparent noncompliance creates a significant threat to the rights and welfare of human subjects, notify relevant State and Federal regulatory agencies and other parties with a direct interest in the agency's action of the deficiencies in the operation of the IRB.
(c) The parent institution is presumed to be responsible for the operation of an IRB, and the Food and Drug Administration will ordinarily direct any administrative action under this subpart against the institution. However, depending on the evidence of responsibility for deficiencies, determined during the investigation, the Food and Drug Administration may restrict its administrative actions to the IRB or to a component of the parent institution determined to be responsible for formal designation of the IRB.

§56.121 Disqualification of an IRB or an institution.
(a) Whenever the IRB or the institution has failed to take adequate steps to correct the noncompliance stated in the letter sent by the agency under §56.120(a), and the Commissioner of Food and Drugs determines that this noncompliance may justify the disqualification of the IRB or of the parent institution, the Commissioner will institute proceedings in accordance with the requirements for a regulatory hearing set forth in part 16.
(b) The Commissioner may disqualify an IRB or the parent institution if the Commissioner determines that:
(1) The IRB has refused or repeatedly failed to comply with any of the regulations set forth in this part, and
(2) The noncompliance adversely affects the rights or welfare of the human subjects in a clinical investigation.
(c) If the Commissioner determines that disqualification is appropriate, the Commissioner will issue an order that explains the basis for the determination and that prescribes
any actions to be taken with regard to ongoing clinical research conducted under the review of the IRB. The Food and Drug Administration will send notice of the disqualification to the IRB and the parent institution. Other parties with a direct interest, such as sponsors and clinical investigators, may also be sent a notice of the disqualification. In addition, the agency may elect to publish a notice of its action in the Federal Register.

(d) The Food and Drug Administration will not approve an application for a research permit for a clinical investigation that is to be under the review of a disqualified IRB or that is to be conducted at a disqualified institution, and it may refuse to consider in support of a marketing permit the data from a clinical investigation that was reviewed by a disqualified IRB as conducted at a disqualified institution, unless the IRB or the parent institution is reinstated as provided in §56.123.

§56.122 Public disclosure of information regarding revocation.
A determination that the Food and Drug Administration has disqualified an institution and the administrative record regarding that determination are disclosable to the public under part 20.

§56.123 Reinstatement of an IRB or an institution.
An IRB or an institution may be reinstated if the Commissioner determines, upon an evaluation of a written submission from the IRB or institution that explains the corrective action that the institution or IRB plans to take, that the IRB or institution has provided adequate assurance that it will operate in compliance with the standards set forth in this part. Notification of reinstatement shall be provided to all persons notified under §56.121(c).

§56.124 Actions alternative or additional to disqualification.
Disqualification of an IRB or of an institution is independent of, and neither in lieu of nor a precondition to, other proceedings or actions authorized by the act. The Food and Drug Administration may, at any time, through the Department of Justice institute any appropriate judicial proceedings (civil or criminal) and any other appropriate regulatory action, in addition to or in lieu of, and before, at the time of, or after, disqualification. The agency may also refer pertinent matters to another Federal, State, or local government agency for any action that that agency determines to be appropriate.
CATEGORIES OF RESEARCH THAT MAY BE REVIEWED BY THE INSTITUTIONAL REVIEW BOARD (IRB) THROUGH AN EXPEDITED REVIEW PROCEDURE

Applicability

(A) Research activities that
   (1) present no more than minimal risk to human subjects, and
   (2) involve only procedures listed in one or more of the following categories, may be reviewed by the IRB through the expedited review procedure authorized by 45 CFR 46.110 and 21 CFR 56.110. The activities listed should not be deemed to be of minimal risk simply because they are included on this list. Inclusion on this list merely means that the activity is eligible for review through the expedited review procedure when the specific circumstances of the proposed research involve no more than minimal risk to human subjects.

(B) The categories in this list apply regardless of the age of subjects, except as noted.

(C) The expedited review procedure may not be used where identification of the subjects and/or their responses would reasonably place them at risk of criminal or civil liability or be damaging to the subjects’ financial standing, employability, insurability, reputation, or be stigmatizing, unless reasonable and appropriate protections will be implemented so that risks related to invasion of privacy and breach of confidentiality are no greater than minimal.

(D) The expedited review procedure may not be used for classified research involving human subjects.

(E) IRBs are reminded that the standard requirements for informed consent (or its waiver, alteration, or exception) apply regardless of the type of review--expedited or convened--utilized by the IRB.

(F) Categories one (1) through seven (7) pertain to both initial and continuing IRB review.

Research Categories

(1) Clinical studies of drugs and medical devices only when condition (a) or (b) is met.
   (a) Research on drugs for which an investigational new drug application (21 CFR Part 312) is not required. (Note: Research on marketed drugs that significantly increases the risks or decreases the acceptability of the risks associated with the use of the product is not eligible for expedited review.)
   (b) Research on medical devices for which
      (i) an investigational device exemption application (21 CFR Part 812) is not required; or
      (ii) the medical device is cleared/approved for marketing and the medical device is being used in accordance with its cleared/approved labeling.

(2) Collection of blood samples by finger stick, heel stick, ear stick, or venipuncture as follows:
(a) from healthy, nonpregnant adults who weigh at least 110 pounds. For these subjects, the amounts drawn may not exceed 550 ml in an 8 week period and collection may not occur more frequently than 2 times per week; or
(b) from other adults and children\(^2\), considering the age, weight, and health of the subjects, the collection procedure, the amount of blood to be collected, and the frequency with which it will be collected. For these subjects, the amount drawn may not exceed the lesser of 50 ml or 3 ml per kg in an 8 week period and collection may not occur more frequently than 2 times per week.

(3) Prospective collection of biological specimens for research purposes by noninvasive means.

Examples:
(a) hair and nail clippings in a nondisfiguring manner;
(b) deciduous teeth at time of exfoliation or if routine patient care indicates a need for extraction;
(c) permanent teeth if routine patient care indicates a need for extraction;
(d) excreta and external secretions (including sweat);
(e) uncannulated saliva collected either in an unstimulated fashion or stimulated by chewing gum base or wax or by applying a dilute citric solution to the tongue;
(f) placenta removed at delivery;
(g) amniotic fluid obtained at the time of rupture of the membrane prior to or during labor;
(h) supra- and subgingival dental plaque and calculus, provided the collection procedure is not more invasive than routine prophylactic scaling of the teeth and the process is accomplished in accordance with accepted prophylactic techniques;
(i) mucosal and skin cells collected by buccal scraping or swab, skin swab, or mouth washings;
(j) sputum collected after saline mist nebulization.

(4) Collection of data through noninvasive procedures (not involving general anesthesia or sedation) routinely employed in clinical practice, excluding procedures involving x-rays or microwaves. Where medical devices are employed, they must be cleared/approved for marketing. (Studies intended to evaluate the safety and effectiveness of the medical device are not generally eligible for expedited review, including studies of cleared medical devices for new indications.)

Examples:
(a) physical sensors that are applied either to the surface of the body or at a distance and do not involve input of significant amounts of energy into the subject or an invasion of the subject’s privacy;
(b) weighing or testing sensory acuity;
(c) magnetic resonance imaging;
(d) electrocardiography, electroencephalography, thermography, detection of naturally occurring radioactivity, electoretinography, ultrasound, diagnostic infrared imaging, doppler blood flow, and echocardiography;
(e) moderate exercise, muscular strength testing, body composition assessment, and flexibility testing where appropriate given the age, weight, and health of the individual.

(5) Research involving materials (data, documents, records, or specimens) that have been collected, or will be collected solely for nonresearch purposes (such as medical treatment or diagnosis). (NOTE: Some research in this category may be exempt from the HHS regulations for the protection of human subjects. 45 CFR 46.101(b)(4). This listing refers only to research that is not exempt.)

(6) Collection of data from voice, video, digital, or image recordings made for research purposes.

(7) Research on individual or group characteristics or behavior (including, but not limited to, research on perception, cognition, motivation, identity, language, communication, cultural beliefs or practices, and social behavior) or research employing survey, interview, oral history, focus group, program evaluation, human factors evaluation, or quality assurance methodologies. (NOTE: Some research in this category may be exempt from the HHS regulations for the protection of human subjects. 45 CFR 46.101(b)(2) and (b)(3). This listing refers only to research that is not exempt.)

(8) Continuing review of research previously approved by the convened IRB as follows:
   (a) where
      (i) the research is permanently closed to the enrollment of new subjects;
      (ii) all subjects have completed all research-related interventions; and
      (iii) the research remains active only for long-term follow-up of subjects;
      or
   (b) where no subjects have been enrolled and no additional risks have been identified; or
   (c) where the remaining research activities are limited to data analysis.

(9) Continuing review of research, not conducted under an investigational new drug application or investigational device exemption where categories two (2) through eight (8) do not apply but the IRB has determined and documented at a convened meeting that the research involves no greater than minimal risk and no additional risks have been identified.

1 An expedited review procedure consists of a review of research involving human subjects by the IRB chairperson or by one or more experienced reviewers designated by the chairperson from among members of the IRB in accordance with the requirements set forth in 45 CFR 46.110.

2 Children are defined in the HHS regulations as "persons who have not attained the legal age for consent to treatments or procedures involved in the research, under the applicable law of the jurisdiction in which the research will be conducted." 45 CFR 46.402(a).
Subpart A--General Provisions

§312.1 Scope.
(a) This part contains procedures and requirements governing the use of investigational new drugs, including procedures and requirements for the submission to, and review by, the Food and Drug Administration of investigational new drug applications (IND's). An investigational new drug for which an IND is in effect in accordance with this part is exempt from the premarketing approval requirements that are otherwise applicable and may be shipped lawfully for the purpose of conducting clinical investigations of that drug.
(b) References in this part to regulations in the Code of Federal Regulations are to chapter I of title 21, unless otherwise noted.

§312.2 Applicability.
(a) Applicability. Except as provided in this section, this part applies to all clinical investigations of products that are subject to section 505 of the Federal Food, Drug, and Cosmetic Act or to the licensing provisions of the Public Health Service Act (58 Stat. 632, as amended (42 U.S.C. 201 et seq.)).
(b) Exemptions.
   (1) The clinical investigation of a drug product that is lawfully marketed in the United States is exempt from the requirements of this part if all the following apply:
      (i) The investigation is not intended to be reported to FDA as a well-controlled study in support of a new indication for use nor intended to be used to support any other significant change in the labeling for the drug;
      (ii) If the drug that is undergoing investigation is lawfully marketed as a prescription drug product, the investigation is not intended to support a significant change in the advertising for the product;
      (iii) The investigation does not involve a route of administration or dosage level or use in a patient population or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product;
      (iv) The investigation is conducted in compliance with the requirements for institutional review set forth in part 56 and with the requirements for informed consent set forth in part 50; and
      (v) The investigation is conducted in compliance with the requirements of §312.7.

   (2)
      (i) A clinical investigation involving an in vitro diagnostic biological product listed in paragraph (b)(2)(ii) of this section is exempt from the requirements of this part if
(a) it is intended to be used in a diagnostic procedure that confirms the diagnosis made by another, medically established, diagnostic product or procedure and
(b) it is shipped in compliance with §312.160.
(ii) In accordance with paragraph (b)(2)(i) of this section, the following products are exempt from the requirements of this part:
(a) blood grouping serum;
(b) reagent red blood cells; and
(c) anti-human globulin.

(3) A drug intended solely for tests in vitro or in laboratory research animals is exempt from the requirements of this part if shipped in accordance with §312.160.

(4) FDA will not accept an application for an investigation that is exempt under the provisions of paragraph (b)(1) of this section.

(5) A clinical investigation involving use of a placebo is exempt from the requirements of this part if the investigation does not otherwise require submission of an IND.

(6) A clinical investigation involving an exception from informed consent under §50.24 of this chapter is not exempt from the requirements of this part.

(c) Bioavailability studies. The applicability of this part to in vivo bioavailability studies in humans is subject to the provisions of §320.31.

(d) Unlabeled indication. This part does not apply to the use in the practice of medicine for an unlabeled indication of a new drug product approved under part 314 or of a licensed biological product.

(e) Guidance. FDA may, on its own initiative, issue guidance on the applicability of this part to particular investigational uses of drugs. On request, FDA will advise on the applicability of this part to a planned clinical investigation.


§312.3 Definitions and interpretations.
(a) The definitions and interpretations of terms contained in section 201 of the Act apply to those terms when used in this part:
(b) The following definitions of terms also apply to this part:
Clinical investigation means any experiment in which a drug is administered or dispensed to, or used involving, one or more human subjects. For the purposes of this part, an experiment is any use of a drug except for the use of a marketed drug in the course of medical practice.
Contract research organization means a person that assumes, as an independent contractor with the sponsor, one or more of the obligations of a sponsor, e.g., design of a protocol, selection or monitoring of investigations, evaluation of reports, and preparation of materials to be submitted to the Food and Drug Administration.
FDA means the Food and Drug Administration.
IND means an investigational new drug application. For purposes of this part, “IND” is synonymous with “Notice of Claimed Investigational Exemption for a New Drug.”

Investigational new drug means a new drug or biological drug that is used in a clinical investigation. The term also includes a biological product that is used in vitro for diagnostic purposes. The terms “investigational drug” and “investigational new drug” are deemed to be synonymous for purposes of this part.

Investigator means an individual who actually conducts a clinical investigation (i.e., under whose immediate direction the drug is administered or dispensed to a subject). In the event an investigation is conducted by a team of individuals, the investigator is the responsible leader of the team. “Subinvestigator” includes any other individual member of that team.

Marketing application means an application for a new drug submitted under section 505(b) of the act or a biologics license application for a biological product submitted under the Public Health Service Act.

Sponsor means a person who takes responsibility for and initiates a clinical investigation. The sponsor may be an individual or pharmaceutical company, governmental agency, academic institution, private organization, or other organization. The sponsor does not actually conduct the investigation unless the sponsor is a sponsor-investigator. A person other than an individual that uses one or more of its own employees to conduct an investigation that it has initiated is a sponsor, not a sponsor-investigator, and the employees are investigators.

Sponsor-Investigator means an individual who both initiates and conducts an investigation, and under whose immediate direction the investigational drug is administered or dispensed. The term does not include any person other than an individual. The requirements applicable to a sponsor-investigator under this part include both those applicable to an investigator and a sponsor.

Subject means a human who participates in an investigation, either as a recipient of the investigational new drug or as a control. A subject may be a healthy human or a patient with a disease.

§312.6 Labeling of an investigational new drug.
(a) The immediate package of an investigational new drug intended for human use shall bear a label with the statement “Caution: New Drug- Limited by Federal (or United States) law to investigational use.”
(b) The label or labeling of an investigational new drug shall not bear any statement that is false or misleading in any particular and shall not represent that the investigational new drug is safe or effective for the purposes for which it is being investigated.

§312.7 Promotion and charging for investigational drugs.
(a) Promotion of an investigational new drug. A sponsor or investigator, or any person acting on behalf of a sponsor or investigator, shall not represent in a promotional
context that an investigational new drug is safe or effective for the purposes for which it is under investigation or otherwise promote the drug. This provision is not intended to restrict the full exchange of scientific information concerning the drug, including dissemination of scientific findings in scientific or lay media. Rather, its intent is to restrict promotional claims of safety or effectiveness of the drug for a use for which it is under investigation and to preclude commercialization of the drug before it is approved for commercial distribution.

(b) Commercial distribution of an investigational new drug. A sponsor or investigator shall not commercially distribute or test market an investigational new drug.

(c) Prolonging an investigation. A sponsor shall not unduly prolong an investigation after finding that the results of the investigation appear to establish sufficient data to support a marketing application.

(d) Charging for and commercialization of investigational drugs—

(1) Clinical trials under an IND. Charging for an investigational drug in a clinical trial under an IND is not permitted without the prior written approval of FDA. In requesting such approval, the sponsor shall provide a full written explanation of why charging is necessary in order for the sponsor to undertake or continue the clinical trial, e.g., why distribution of the drug to test subjects should not be considered part of the normal cost of doing business.

(2) Treatment protocol or treatment IND. A sponsor or investigator may charge for an investigational drug for a treatment use under a treatment protocol or treatment IND provided:

   (i) There is adequate enrollment in the ongoing clinical investigations under the authorized IND;

   (ii) charging does not constitute commercial marketing of a new drug for which a marketing application has not been approved;

   (iii) the drug is not being commercially promoted or advertised; and

   (iv) the sponsor of the drug is actively pursuing marketing approval with due diligence. FDA must be notified in writing in advance of commencing any such charges, in an information amendment submitted under §312.31. Authorization for charging goes into effect automatically 30 days after receipt by FDA of the information amendment, unless the sponsor is notified to the contrary.

(3) Noncommercialization of investigational drug. Under this section, the sponsor may not commercialize an investigational drug by charging a price larger than that necessary to recover costs of manufacture, research, development, and handling of the investigational drug.

(4) Withdrawal of authorization. Authorization to charge for an investigational drug under this section may be withdrawn by FDA if the agency finds that the conditions underlying the authorization are no longer satisfied.


§312.10 Waivers.

(a) A sponsor may request FDA to waive applicable requirement under this part. A waiver request may be submitted either in an IND or in an information amendment to an IND. In an emergency, a request may be made by telephone or other rapid
communication means. A waiver request is required to contain at least one of the following:
(1) An explanation why the sponsor's compliance with the requirement is unnecessary or cannot be achieved;
(2) A description of an alternative submission or course of action that satisfies the purpose of the requirement; or
(3) Other information justifying a waiver.

(b) FDA may grant a waiver if it finds that the sponsor's noncompliance would not pose a significant and unreasonable risk to human subjects of the investigation and that one of the following is met:
(1) The sponsor's compliance with the requirement is unnecessary for the agency to evaluate the application, or compliance cannot be achieved;
(2) The sponsor's proposed alternative satisfies the requirement; or
(3) The applicant's submission otherwise justifies a waiver.


Subpart B--Investigational New Drug Application (IND)

§312.20 Requirement for an IND.
(a) A sponsor shall submit an IND to FDA if the sponsor intends to conduct a clinical investigation with an investigational new drug that is subject to §312.2.
(b) A sponsor shall not begin a clinical investigation subject to §312.2 until the investigation is subject to an IND which is in effect in accordance with §312.40.
(c) A sponsor shall submit a separate IND for any clinical investigation involving an exception from informed consent under §50.24 of this chapter. Such a clinical investigation is not permitted to proceed without the prior written authorization from FDA. FDA shall provide a written determination 30 days after FDA receives the IND or earlier.


§312.21 Phases of an investigation.
An IND may be submitted for one or more phases of an investigation. The clinical investigation of a previously untested drug is generally divided into three phases. Although in general the phases are conducted sequentially, they may overlap. These three phases of an investigation are as follows:
(a) Phase 1.
   (1) Phase 1 includes the initial introduction of an investigational new drug into humans. Phase 1 studies are typically closely monitored and may be conducted in patients or normal volunteer subjects. These studies are designed to determine the metabolism and pharmacologic actions of the drug in humans, the side effects associated with increasing doses, and, if possible, to gain early evidence on effectiveness. During Phase 1, sufficient information about the drug's pharmacokinetics and pharmacological effects should be obtained to permit the design of well-controlled, scientifically valid, Phase 2 studies. The
total number of subjects and patients included in Phase 1 studies varies with the drug, but is generally in the range of 20 to 80.

(2) Phase 1 studies also include studies of drug metabolism, structure-activity relationships, and mechanism of action in humans, as well as studies in which investigational drugs are used as research tools to explore biological phenomena or disease processes.

(b) Phase 2. Phase 2 includes the controlled clinical studies conducted to evaluate the effectiveness of the drug for a particular indication or indications in patients with the disease or condition under study and to determine the common short-term side effects and risks associated with the drug. Phase 2 studies are typically well controlled, closely monitored, and conducted in a relatively small number of patients, usually involving no more than several hundred subjects.

(c) Phase 3. Phase 3 studies are expanded controlled and uncontrolled trials. They are performed after preliminary evidence suggesting effectiveness of the drug has been obtained, and are intended to gather the additional information about effectiveness and safety that is needed to evaluate the overall benefit-risk relationship of the drug and to provide an adequate basis for physician labeling. Phase 3 studies usually include from several hundred to several thousand subjects.

§312.22 General principles of the IND submission.

(a) FDA's primary objectives in reviewing an IND are, in all phases of the investigation, to assure the safety and rights of subjects, and, in Phase 2 and 3, to help assure that the quality of the scientific evaluation of drugs is adequate to permit an evaluation of the drug's effectiveness and safety. Therefore, although FDA's review of Phase 1 submissions will focus on assessing the safety of Phase 1 investigations, FDA's review of Phases 2 and 3 submissions will also include an assessment of the scientific quality of the clinical investigations and the likelihood that the investigations will yield data capable of meeting statutory standards for marketing approval.

(b) The amount of information on a particular drug that must be submitted in an IND to assure the accomplishment of the objectives described in paragraph (a) of this section depends upon such factors as the novelty of the drug, the extent to which it has been studied previously, the known or suspected risks, and the developmental phase of the drug.

(c) The central focus of the initial IND submission should be on the general investigational plan and the protocols for specific human studies. Subsequent amendments to the IND that contain new or revised protocols should build logically on previous submissions and should be supported by additional information, including the results of animal toxicology studies or other human studies as appropriate. Annual reports to the IND should serve as the focus for reporting the status of studies being conducted under the IND and should update the general investigational plan for the coming year.

(d) The IND format set forth in §312.23 should be followed routinely by sponsors in the interest of fostering an efficient review of applications. Sponsors are expected to exercise considerable discretion, however, regarding the content of information submitted in each section, depending upon the kind of drug being studied and the nature of the available information. Section 312.23 outlines the information needed.
for a commercially sponsored IND for a new molecular entity. A sponsor-investigator who uses, as a research tool, an investigational new drug that is already subject to a manufacturer's IND or marketing application should follow the same general format, but ordinarily may, if authorized by the manufacturer, refer to the manufacturer's IND or marketing application in providing the technical information supporting the proposed clinical investigation. A sponsor-investigator who uses an investigational drug not subject to a manufacturer's IND or marketing application is ordinarily required to submit all technical information supporting the IND, unless such information may be referenced from the scientific literature.

§312.23 IND content and format.

(a) A sponsor who intends to conduct a clinical investigation subject to this part shall submit an “Investigational New Drug Application” (IND) including, in the following order:

1. Cover sheet (Form FDA-1571). A cover sheet for the application containing the following:
   - (i) The name, address, and telephone number of the sponsor, the date of the application, and the name of the investigational new drug.
   - (ii) Identification of the phase or phases of the clinical investigation to be conducted.
   - (iii) A commitment not to begin clinical investigations until an IND covering the investigations is in effect.
   - (iv) A commitment that an Institutional Review Board (IRB) that complies with the requirements set forth in part 56 will be responsible for the initial and continuing review and approval of each of the studies in the proposed clinical investigation and that the investigator will report to the IRB proposed changes in the research activity in accordance with the requirements of part 56.
   - (v) A commitment to conduct the investigation in accordance with all other applicable regulatory requirements.
   - (vi) The name and title of the person responsible for monitoring the conduct and progress of the clinical investigations.
   - (vii) The name(s) and title(s) of the person(s) responsible under §312.32 for review and evaluation of information relevant to the safety of the drug.
   - (viii) If a sponsor has transferred any obligations for the conduct of any clinical study to a contract research organization, a statement containing the name and address of the contract research organization, identification of the clinical study, and a listing of the obligations transferred. If all obligations governing the conduct of the study have been transferred, a general statement of this transfer--in lieu of a listing of the specific obligations transferred--may be submitted.
   - (ix) The signature of the sponsor or the sponsor's authorized representative. If the person signing the application does not reside or have a place of business within the United States, the IND is required to contain the name and address of, and be countersigned by, an attorney, agent, or other
authorized official who resides or maintains a place of business within the United States.

(2) A table of contents.
(3) Introductory statement and general investigational plan.
   (i) A brief introductory statement giving the name of the drug and all active ingredients, the drug's pharmacological class, the structural formula of the drug (if known), the formulation of the dosage form(s) to be used, the route of administration, and the broad objectives and planned duration of the proposed clinical investigation(s).
   (ii) A brief summary of previous human experience with the drug, with reference to other IND's if pertinent, and to investigational or marketing experience in other countries that may be relevant to the safety of the proposed clinical investigation(s).
   (iii) If the drug has been withdrawn from investigation or marketing in any country for any reason related to safety or effectiveness, identification of the country(ies) where the drug was withdrawn and the reasons for the withdrawal.
   (iv) A brief description of the overall plan for investigating the drug product for the following year. The plan should include the following: (a) The rationale for the drug or the research study; (b) the indication(s) to be studied; (c) the general approach to be followed in evaluating the drug; (d) the kinds of clinical trials to be conducted in the first year following the submission (if plans are not developed for the entire year, the sponsor should so indicate); (e) the estimated number of patients to be given the drug in those studies; and (f) any risks of particular severity or seriousness anticipated on the basis of the toxicological data in animals or prior studies in humans with the drug or related drugs.

(4) [Reserved]

(5) Investigator's brochure. If required under §312.55, a copy of the investigator's brochure, containing the following information:
   (i) A brief description of the drug substance and the formulation, including the structural formula, if known.
   (ii) A summary of the pharmacological and toxicological effects of the drug in animals and, to the extent known, in humans.
   (iii) A summary of the pharmacokinetics and biological disposition of the drug in animals and, if known, in humans.
   (iv) A summary of information relating to safety and effectiveness in humans obtained from prior clinical studies. (Reprints of published articles on such studies may be appended when useful.)
   (v) A description of possible risks and side effects to be anticipated on the basis of prior experience with the drug under investigation or with related drugs, and of precautions or special monitoring to be done as part of the investigational use of the drug.

(6) Protocols.
   (i) A protocol for each planned study. (Protocols for studies not submitted initially in the IND should be submitted in accordance with §312.30(a).)
In general, protocols for Phase 1 studies may be less detailed and more flexible than protocols for Phase 2 and 3 studies. Phase 1 protocols should be directed primarily at providing an outline of the investigation—an estimate of the number of patients to be involved, a description of safety exclusions, and a description of the dosing plan including duration, dose, or method to be used in determining dose—and should specify in detail only those elements of the study that are critical to safety, such as necessary monitoring of vital signs and blood chemistries. Modifications of the experimental design of Phase 1 studies that do not affect critical safety assessments are required to be reported to FDA only in the annual report.

(ii) In Phases 2 and 3, detailed protocols describing all aspects of the study should be submitted. A protocol for a Phase 2 or 3 investigation should be designed in such a way that, if the sponsor anticipates that some deviation from the study design may become necessary as the investigation progresses, alternatives or contingencies to provide for such deviation are built into the protocols at the outset. For example, a protocol for a controlled short-term study might include a plan for an early crossover of nonresponders to an alternative therapy.

(iii) A protocol is required to contain the following, with the specific elements and detail of the protocol reflecting the above distinctions depending on the phase of study:

(a) A statement of the objectives and purpose of the study.
(b) The name and address and a statement of the qualifications (curriculum vitae or other statement of qualifications) of each investigator, and the name of each subinvestigator (e.g., research fellow, resident) working under the supervision of the investigator; the name and address of the research facilities to be used; and the name and address of each reviewing Institutional Review Board.
(c) The criteria for patient selection and for exclusion of patients and an estimate of the number of patients to be studied.
(d) A description of the design of the study, including the kind of control group to be used, if any, and a description of methods to be used to minimize bias on the part of subjects, investigators, and analysts.
(e) The method for determining the dose(s) to be administered, the planned maximum dosage, and the duration of individual patient exposure to the drug.
(f) A description of the observations and measurements to be made to fulfill the objectives of the study.
(g) A description of clinical procedures, laboratory tests, or other measures to be taken to monitor the effects of the drug in human subjects and to minimize risk.

(7) Chemistry, manufacturing, and control information.

(i) As appropriate for the particular investigations covered by the IND, a section describing the composition, manufacture, and control of the drug substance and the drug product. Although in each phase of the
investigation sufficient information is required to be submitted to assure the proper identification, quality, purity, and strength of the investigational drug, the amount of information needed to make that assurance will vary with the phase of the investigation, the proposed duration of the investigation, the dosage form, and the amount of information otherwise available. FDA recognizes that modifications to the method of preparation of the new drug substance and dosage form and changes in the dosage form itself are likely as the investigation progresses. Therefore, the emphasis in an initial Phase 1 submission should generally be placed on the identification and control of the raw materials and the new drug substance. Final specifications for the drug substance and drug product are not expected until the end of the investigational process.

(ii) It should be emphasized that the amount of information to be submitted depends upon the scope of the proposed clinical investigation. For example, although stability data are required in all phases of the IND to demonstrate that the new drug substance and drug product are within acceptable chemical and physical limits for the planned duration of the proposed clinical investigation, if very short-term tests are proposed, the supporting stability data can be correspondingly limited.

(iii) As drug development proceeds and as the scale or production is changed from the pilot-scale production appropriate for the limited initial clinical investigations to the larger-scale production needed for expanded clinical trials, the sponsor should submit information amendments to supplement the initial information submitted on the chemistry, manufacturing, and control processes with information appropriate to the expanded scope of the investigation.

(iv) Reflecting the distinctions described in this paragraph (a)(7), and based on the phase(s) to be studied, the submission is required to contain the following:

(a) Drug substance. A description of the drug substance, including its physical, chemical, or biological characteristics; the name and address of its manufacturer; the general method of preparation of the drug substance; the acceptable limits and analytical methods used to assure the identity, strength, quality, and purity of the drug substance; and information sufficient to support stability of the drug substance during the toxicological studies and the planned clinical studies. Reference to the current edition of the United States Pharmacopeia--National Formulary may satisfy relevant requirements in this paragraph.

(b) Drug product. A list of all components, which may include reasonable alternatives for inactive compounds, used in the manufacture of the investigational drug product, including both those components intended to appear in the drug product and those which may not appear but which are used in the manufacturing process, and, where applicable, the quantitative composition of the investigational drug product, including any reasonable variations that may be expected during the investigational stage; the name and address of the drug
product manufacturer; a brief general description of the manufacturing
and packaging procedure as appropriate for the product; the acceptable
limits and analytical methods used to assure the identity, strength,
quality, and purity of the drug product; and information sufficient to
assure the product's stability during the planned clinical studies.
Reference to the current edition of the United States Pharmacopeia--
National Formulary may satisfy certain requirements in this paragraph.
(c) A brief general description of the composition, manufacture, and
control of any placebo used in a controlled clinical trial.
(d) Labeling. A copy of all labels and labeling to be provided to each
investigator.
(e) Environmental analysis requirements. A claim for categorical
exclusion under §25.30 or 25.31 or an environmental assessment under
§25.40.
(8) Pharmacology and toxicology information. Adequate information about
pharmacological and toxicological studies of the drug involving laboratory
animals or in vitro, on the basis of which the sponsor has concluded that it is
reasonably safe to conduct the proposed clinical investigations. The kind,
duration, and scope of animal and other tests required varies with the duration
and nature of the proposed clinical investigations. Guidance documents are
available from FDA that describe ways in which these requirements may be
met. Such information is required to include the identification and qualifications
of the individuals who evaluated the results of such studies and concluded that it
is reasonably safe to begin the proposed investigations and a statement of where
the investigations were conducted and where the records are available for
inspection. As drug development proceeds, the sponsor is required to submit
informational amendments, as appropriate, with additional information pertinent
to safety.
(i) Pharmacology and drug disposition. A section describing the
pharmacological effects and mechanism(s) of action of the drug in
animals, and information on the absorption, distribution, metabolism, and
excretion of the drug, if known.
(ii) Toxicology.
(a) An integrated summary of the toxicological effects of the drug in
animals and in vitro. Depending on the nature of the drug and the
phase of the investigation, the description is to include the results of
acute, subacute, and chronic toxicity tests; tests of the drug's effects on
reproduction and the developing fetus; any special toxicity test related
to the drug's particular mode of administration or conditions of use
(e.g., inhalation, dermal, or ocular toxicology); and any in vitro studies
intended to evaluate drug toxicity.
(b) For each toxicology study that is intended primarily to support the
safety of the proposed clinical investigation, a full tabulation of data
suitable for detailed review.
(iii) For each nonclinical laboratory study subject to the good laboratory
practice regulations under part 58, a statement that the study was
conducted in compliance with the good laboratory practice regulations in part 58, or, if the study was not conducted in compliance with those regulations, a brief statement of the reason for the noncompliance.

(9) Previous human experience with the investigational drug. A summary of previous human experience known to the applicant, if any, with the investigational drug. The information is required to include the following:

(i) If the investigational drug has been investigated or marketed previously, either in the United States or other countries, detailed information about such experience that is relevant to the safety of the proposed investigation or to the investigation's rationale. If the drug has been the subject of controlled trials, detailed information on such trials that is relevant to an assessment of the drug's effectiveness for the proposed investigational use(s) should also be provided. Any published material that is relevant to the safety of the proposed investigation or to an assessment of the drug's effectiveness for its proposed investigational use should be provided in full. Published material that is less directly relevant may be supplied by a bibliography.

(ii) If the drug is a combination of drugs previously investigated or marketed, the information required under paragraph (a)(9)(i) of this section should be provided for each active drug component. However, if any component in such combination is subject to an approved marketing application or is otherwise lawfully marketed in the United States, the sponsor is not required to submit published material concerning that active drug component unless such material relates directly to the proposed investigational use (including publications relevant to component-component interaction).

(iii) If the drug has been marketed outside the United States, a list of the countries in which the drug has been marketed and a list of the countries in which the drug has been withdrawn from marketing for reasons potentially related to safety or effectiveness.

(10) Additional information. In certain applications, as described below, information on special topics may be needed. Such information shall be submitted in this section as follows:

(i) Drug dependence and abuse potential. If the drug is a psychotropic substance or otherwise has abuse potential, a section describing relevant clinical studies and experience and studies in test animals.

(ii) Radioactive drugs. If the drug is a radioactive drug, sufficient data from animal or human studies to allow a reasonable calculation of radiation-absorbed dose to the whole body and critical organs upon administration to a human subject. Phase 1 studies of radioactive drugs must include studies which will obtain sufficient data for dosimetry calculations.

(iii) Pediatric studies. Plans for assessing pediatric safety and effectiveness.

(iv) Other information. A brief statement of any other information that would aid evaluation of the proposed clinical investigations with respect to their safety or their design and potential as controlled clinical trials to support marketing of the drug.
(11) Relevant information. If requested by FDA, any other relevant information needed for review of the application.

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

(c) Material in a foreign language. The sponsor shall submit an accurate and complete English translation of each part of the IND that is not in English. The sponsor shall also submit a copy of each original literature publication for which an English translation is submitted.

(d) Number of copies. The sponsor shall submit an original and two copies of all submissions to the IND file, including the original submission and all amendments and reports.

(e) Numbering of IND submissions. Each submission relating to an IND is required to be numbered serially using a single, three-digit serial number. The initial IND is required to be numbered 000; each subsequent submission (e.g., amendment, report, or correspondence) is required to be numbered chronologically in sequence.

(f) Identification of exception from informed consent. If the investigation involves an exception from informed consent under §50.24 of this chapter, the sponsor shall prominently identify on the cover sheet that the investigation is subject to the requirements in §50.24 of this chapter.


§312.30 Protocol amendments.

Once an IND is in effect, a sponsor shall amend it as needed to ensure that the clinical investigations are conducted according to protocols included in the application. This section sets forth the provisions under which new protocols may be submitted and changes in previously submitted protocols may be made. Whenever a sponsor intends to conduct a clinical investigation with an exception from informed consent for emergency research as set forth in §50.24 of this chapter, the sponsor shall submit a separate IND for such investigation.

(a) New protocol. Whenever a sponsor intends to conduct a study that is not covered by a protocol already contained in the IND, the sponsor shall submit to FDA a protocol amendment containing the protocol for the study. Such study may begin provided two conditions are met:

(1) The sponsor has submitted the protocol to FDA for its review; and

(2) the protocol has been approved by the Institutional Review Board (IRB) with responsibility for review and approval of the study in accordance with the requirements of part 56. The sponsor may comply with these two conditions in either order.

(b) Changes in a protocol.
(1) A sponsor shall submit a protocol amendment describing any change in a Phase 1 protocol that significantly affects the safety of subjects or any change in a Phase 2 or 3 protocol that significantly affects the safety of subjects, the scope of the investigation, or the scientific quality of the study. Examples of changes requiring an amendment under this paragraph include:
(i) Any increase in drug dosage or duration of exposure of individual subjects to the drug beyond that in the current protocol, or any significant increase in the number of subjects under study.
(ii) Any significant change in the design of a protocol (such as the addition or dropping of a control group).
(iii) The addition of a new test or procedure that is intended to improve monitoring for, or reduce the risk of, a side effect or adverse event; or the dropping of a test intended to monitor safety.

(2) (i) A protocol change under paragraph (b)(1) of this section may be made provided two conditions are met:
(a) The sponsor has submitted the change to FDA for its review; and
(b) The change has been approved by the IRB with responsibility for review and approval of the study. The sponsor may comply with these two conditions in either order.
(ii) Notwithstanding paragraph (b)(2)(i) of this section, a protocol change intended to eliminate an apparent immediate hazard to subjects may be implemented immediately provided FDA is subsequently notified by protocol amendment and the reviewing IRB is notified in accordance with §56.104(c).

(c) New investigator. A sponsor shall submit a protocol amendment when a new investigator is added to carry out a previously submitted protocol, except that a protocol amendment is not required when a licensed practitioner is added in the case of a treatment protocol under §312.34. Once the investigator is added to the study, the investigational drug may be shipped to the investigator and the investigator may begin participating in the study. The sponsor shall notify FDA of the new investigator within 30 days of the investigator being added.

(d) Content and format. A protocol amendment is required to be prominently identified as such (i.e., “Protocol Amendment: New Protocol”, “Protocol Amendment: Change in Protocol”, or “Protocol Amendment: New Investigator”), and to contain the following:
(1) (i) In the case of a new protocol, a copy of the new protocol and a brief description of the most clinically significant differences between it and previous protocols.
(ii) In the case of a change in protocol, a brief description of the change and reference (date and number) to the submission that contained the protocol.
(iii) In the case of a new investigator, the investigator's name, the qualifications to conduct the investigation, reference to the previously submitted protocol, and all additional information about the investigator's study as is required under §312.23(a)(6)(iii)(b).
(2) Reference, if necessary, to specific technical information in the IND or in a concurrently submitted information amendment to the IND that the sponsor relies on to support any clinically significant change in the new or amended protocol. If the reference is made to supporting information already in the IND, the sponsor shall identify by name, reference number, volume, and page number the location of the information.

(3) If the sponsor desires FDA to comment on the submission, a request for such comment and the specific questions FDA’s response should address.

(e) When submitted. A sponsor shall submit a protocol amendment for a new protocol or a change in protocol before its implementation. Protocol amendments to add a new investigator or to provide additional information about investigators may be grouped and submitted at 30-day intervals. When several submissions of new protocols or protocol changes are anticipated during a short period, the sponsor is encouraged, to the extent feasible, to include these all in a single submission.

§312.31 Information amendments.

(a) Requirement for information amendment. A sponsor shall report in an information amendment essential information on the IND that is not within the scope of a protocol amendment, IND safety reports, or annual report. Examples of information requiring an information amendment include:

(1) New toxicology, chemistry, or other technical information; or

(2) A report regarding the discontinuance of a clinical investigation.

(b) Content and format of an information amendment. An information amendment is required to bear prominent identification of its contents (e.g., “Information Amendment: Chemistry, Manufacturing, and Control”, “Information Amendment: Pharmacology-Toxicology”, “Information Amendment: Clinical”), and to contain the following:

(1) A statement of the nature and purpose of the amendment.

(2) An organized submission of the data in a format appropriate for scientific review.

(3) If the sponsor desires FDA to comment on an information amendment, a request for such comment.

(c) When submitted. Information amendments to the IND should be submitted as necessary but, to the extent feasible, not more than every 30 days.

§312.32 IND safety reports.

(a) Definitions. The following definitions of terms apply to this section:

Associated with the use of the drug. There is a reasonable possibility that the experience may have been caused by the drug.

Disability. A substantial disruption of a person's ability to conduct normal life functions.
Life-threatening adverse drug experience. Any adverse drug experience that places the patient or subject, in the view of the investigator, at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction that, had it occurred in a more severe form, might have caused death.

Serious adverse drug experience: Any adverse drug experience occurring at any dose that results in any of the following outcomes: Death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Unexpected adverse drug experience: Any adverse drug experience, the specificity or severity of which is not consistent with the current investigator brochure; or, if an investigator brochure is not required or available, the specificity or severity of which is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the investigator brochure only referred to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the investigator brochure only listed cerebral vascular accidents. “Unexpected,” as used in this definition, refers to an adverse drug experience that has not been previously observed (e.g., included in the investigator brochure) rather than from the perspective of such experience not being anticipated from the pharmacological properties of the pharmaceutical product.

(b) Review of safety information. The sponsor shall promptly review all information relevant to the safety of the drug obtained or otherwise received by the sponsor from any source, foreign or domestic, including information derived from any clinical or epidemiological investigations, animal investigations, commercial marketing experience, reports in the scientific literature, and unpublished scientific papers, as well as reports from foreign regulatory authorities that have not already been previously reported to the agency by the sponsor.

(c) IND safety reports.

(1) Written reports--
   (i) The sponsor shall notify FDA and all participating investigators in a written IND safety report of:
      (A) Any adverse experience associated with the use of the drug that is both serious and unexpected; or
(B) Any finding from tests in laboratory animals that suggests a significant risk for human subjects including reports of mutagenicity, teratogenicity, or carcinogenicity. Each notification shall be made as soon as possible and in no event later than 15 calendar days after the sponsor's initial receipt of the information. Each written notification may be submitted on FDA Form 3500A or in a narrative format (foreign events may be submitted either on an FDA Form 3500A or, if preferred, on a CIOMS I form; reports from animal or epidemiological studies shall be submitted in a narrative format) and shall bear prominent identification of its contents, i.e., “IND Safety Report.” Each written notification to FDA shall be transmitted to the FDA new drug review division in the Center for Drug Evaluation and Research or the product review division in the Center for Biologics Evaluation and Research that has responsibility for review of the IND. If FDA determines that additional data are needed, the agency may require further data to be submitted.

(ii) In each written IND safety report, the sponsor shall identify all safety reports previously filed with the IND concerning a similar adverse experience, and shall analyze the significance of the adverse experience in light of the previous, similar reports.

(2) Telephone and facsimile transmission safety reports. The sponsor shall also notify FDA by telephone or by facsimile transmission of any unexpected fatal or life-threatening experience associated with the use of the drug as soon as possible but in no event later than 7 calendar days after the sponsor's initial receipt of the information. Each telephone call or facsimile transmission to FDA shall be transmitted to the FDA new drug review division in the Center for Drug Evaluation and Research or the product review division in the Center for Biologics Evaluation and Research that has responsibility for review of the IND.

(3) Reporting format or frequency. FDA may request a sponsor to submit IND safety reports in a format or at a frequency different than that required under this paragraph. The sponsor may also propose and adopt a different reporting format or frequency if the change is agreed to in advance by the director of the new drug review division in the Center for Drug Evaluation and Research or the director of the products review division in the Center for Biologics Evaluation and Research which is responsible for review of the IND.

(4) A sponsor of a clinical study of a marketed drug is not required to make a safety report for any adverse experience associated with use of the drug that is not from the clinical study itself.

(d) Followup.

(1) The sponsor shall promptly investigate all safety information received by it.

(2) Followup information to a safety report shall be submitted as soon as the relevant information is available.

(3) If the results of a sponsor's investigation show that an adverse drug experience not initially determined to be reportable under paragraph (c) of this section is so reportable, the sponsor shall report such experience in a written safety report as
soon as possible, but in no event later than 15 calendar days after the
determination is made.
(4) Results of a sponsor's investigation of other safety information shall be submitted,
as appropriate, in an information amendment or annual report.
(e) Disclaimer. A safety report or other information submitted by a sponsor under this
part (and any release by FDA of that report or information) does not necessarily
reflect a conclusion by the sponsor or FDA that the report or information constitutes
an admission that the drug caused or contributed to an adverse experience. A sponsor
need not admit, and may deny, that the report or information submitted by the sponsor
constitutes an admission that the drug caused or contributed to an adverse experience.

FR 52250, Oct. 7, 1997; 67 FR 9585, Mar. 4, 2002]

§312.33 Annual reports.
A sponsor shall within 60 days of the anniversary date that the IND went into effect,
submit a brief report of the progress of the investigation that includes:
(a) Individual study information. A brief summary of the status of each study in progress
and each study completed during the previous year. The summary is required to
include the following information for each study:
(1) The title of the study (with any appropriate study identifiers such as protocol
number), its purpose, a brief statement identifying the patient population, and a
statement as to whether the study is completed.
(2) The total number of subjects initially planned for inclusion in the study; the
number entered into the study to date, tabulated by age group, gender, and race;
the number whose participation in the study was completed as planned; and the
number who dropped out of the study for any reason.
(3) If the study has been completed, or if interim results are known, a brief
description of any available study results.
(b) Summary information. Information obtained during the previous year's clinical and
nonclinical investigations, including:
(1) A narrative or tabular summary showing the most frequent and most serious
adverse experiences by body system.
(2) A summary of all IND safety reports submitted during the past year.
(3) A list of subjects who died during participation in the investigation, with the cause
of death for each subject.
(4) A list of subjects who dropped out during the course of the investigation in
association with any adverse experience, whether or not thought to be drug
related.
(5) A brief description of what, if anything, was obtained that is pertinent to an
understanding of the drug's actions, including, for example, information about
dose response, information from controlled trails, and information about
bioavailability.
(6) A list of the preclinical studies (including animal studies) completed or in
progress during the past year and a summary of the major preclinical findings.
(7) A summary of any significant manufacturing or microbiological changes made
during the past year.
(c) A description of the general investigational plan for the coming year to replace that submitted 1 year earlier. The general investigational plan shall contain the information required under §312.23(a)(3)(iv).

(d) If the investigator brochure has been revised, a description of the revision and a copy of the new brochure.

(e) A description of any significant Phase 1 protocol modifications made during the previous year and not previously reported to the IND in a protocol amendment.

(f) A brief summary of significant foreign marketing developments with the drug during the past year, such as approval of marketing in any country or withdrawal or suspension from marketing in any country.

(g) If desired by the sponsor, a log of any outstanding business with respect to the IND for which the sponsor requests or expects a reply, comment, or meeting.


§312.34 Treatment use of an investigational new drug.

(a) General. A drug that is not approved for marketing may be under clinical investigation for a serious or immediately life-threatening disease condition in patients for whom no comparable or satisfactory alternative drug or other therapy is available. During the clinical investigation of the drug, it may be appropriate to use the drug in the treatment of patients not in the clinical trials, in accordance with a treatment protocol or treatment IND. The purpose of this section is to facilitate the availability of promising new drugs to desperately ill patients as early in the drug development process as possible, before general marketing begins, and to obtain additional data on the drug's safety and effectiveness. In the case of a serious disease, a drug ordinarily may be made available for treatment use under this section during Phase 3 investigations or after all clinical trials have been completed; however, in appropriate circumstances, a drug may be made available for treatment use during Phase 2. In the case of an immediately life-threatening disease, a drug may be made available for treatment use under this section earlier than Phase 3, but ordinarily not earlier than Phase 2. For purposes of this section, the “treatment use” of a drug includes the use of a drug for diagnostic purposes. If a protocol for an investigational drug meets the criteria of this section, the protocol is to be submitted as a treatment protocol under the provisions of this section.

(b) Criteria.

(1) FDA shall permit an investigational drug to be used for a treatment use under a treatment protocol or treatment IND if:

(i) The drug is intended to treat a serious or immediately life-threatening disease;

(ii) There is no comparable or satisfactory alternative drug or other therapy available to treat that stage of the disease in the intended patient population;

(iii) The drug is under investigation in a controlled clinical trial under an IND in effect for the trial, or all clinical trials have been completed; and

(iv) The sponsor of the controlled clinical trial is actively pursuing marketing approval of the investigational drug with due diligence.

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(2) Serious disease. For a drug intended to treat a serious disease, the Commissioner may deny a request for treatment use under a treatment protocol or treatment IND if there is insufficient evidence of safety and effectiveness to support such use.

(3) Immediately life-threatening disease.
   (i) For a drug intended to treat an immediately life-threatening disease, the Commissioner may deny a request for treatment use of an investigational drug under a treatment protocol or treatment IND if the available scientific evidence, taken as a whole, fails to provide a reasonable basis for concluding that the drug:
      (A) May be effective for its intended use in its intended patient population; or
      (B) Would not expose the patients to whom the drug is to be administered to an unreasonable and significant additional risk of illness or injury.
   (ii) For the purpose of this section, an “immediately life-threatening” disease means a stage of a disease in which there is a reasonable likelihood that death will occur within a matter of months or in which premature death is likely without early treatment.

(c) Safeguards. Treatment use of an investigational drug is conditioned on the sponsor and investigators complying with the safeguards of the IND process, including the regulations governing informed consent (21 CFR part 50) and institutional review boards (21 CFR part 56) and the applicable provisions of part 312, including distribution of the drug through qualified experts, maintenance of adequate manufacturing facilities, and submission of IND safety reports.

(d) Clinical hold. FDA may place on clinical hold a proposed or ongoing treatment protocol or treatment IND in accordance with §312.42.


§312.35 Submissions for treatment use.

(a) Treatment protocol submitted by IND sponsor. Any sponsor of a clinical investigation of a drug who intends to sponsor a treatment use for the drug shall submit to FDA a treatment protocol under §312.34 if the sponsor believes the criteria of §312.34 are satisfied. If a protocol is not submitted under §312.34, but FDA believes that the protocol should have been submitted under this section, FDA may deem the protocol to be submitted under §312.34. A treatment use under a treatment protocol may begin 30 days after FDA receives the protocol or on earlier notification by FDA that the treatment use described in the protocol may begin.

(1) A treatment protocol is required to contain the following:
   (i) The intended use of the drug.
   (ii) An explanation of the rationale for use of the drug, including, as appropriate, either a list of what available regimens ordinarily should be tried before using the investigational drug or an explanation of why the use of the investigational drug is preferable to the use of available marketed treatments.
   (iii) A brief description of the criteria for patient selection.
   (iv) The method of administration of the drug and the dosages.
(v) A description of clinical procedures, laboratory tests, or other measures to monitor the effects of the drug and to minimize risk.

(2) A treatment protocol is to be supported by the following:
   (i) Informational brochure for supplying to each treating physician.
   (ii) The technical information that is relevant to safety and effectiveness of the drug for the intended treatment purpose. Information contained in the sponsor's IND may be incorporated by reference.
   (iii) A commitment by the sponsor to assure compliance of all participating investigators with the informed consent requirements of 21 CFR part 50.

(3) A licensed practitioner who receives an investigational drug for treatment use under a treatment protocol is an “investigator” under the protocol and is responsible for meeting all applicable investigator responsibilities under this part and 21 CFR parts 50 and 56.

(b) Treatment IND submitted by licensed practitioner.

(1) If a licensed medical practitioner wants to obtain an investigational drug subject to a controlled clinical trial for a treatment use, the practitioner should first attempt to obtain the drug from the sponsor of the controlled trial under a treatment protocol. If the sponsor of the controlled clinical investigation of the drug will not establish a treatment protocol for the drug under paragraph (a) of this section, the licensed medical practitioner may seek to obtain the drug from the sponsor and submit a treatment IND to FDA requesting authorization to use the investigational drug for treatment use. A treatment use under a treatment IND may begin 30 days after FDA receives the IND or on earlier notification by FDA that the treatment use under the IND may begin. A treatment IND is required to contain the following:
   (i) A cover sheet (Form FDA 1571) meeting §312.23(g)(1).
   (ii) Information (when not provided by the sponsor) on the drug's chemistry, manufacturing, and controls, and prior clinical and nonclinical experience with the drug submitted in accordance with §312.23. A sponsor of a clinical investigation subject to an IND who supplies an investigational drug to a licensed medical practitioner for purposes of a separate treatment clinical investigation shall be deemed to authorize the incorporation-by-reference of the technical information contained in the sponsor's IND into the medical practitioner's treatment IND.
   (iii) A statement of the steps taken by the practitioner to obtain the drug under a treatment protocol from the drug sponsor.
   (iv) A treatment protocol containing the same information listed in paragraph (a)(1) of this section.
   (v) A statement of the practitioner's qualifications to use the investigational drug for the intended treatment use.
   (vi) The practitioner's statement of familiarity with information on the drug's safety and effectiveness derived from previous clinical and nonclinical experience with the drug.
   (vii) Agreement to report to FDA safety information in accordance with §312.32.
(2) A licensed practitioner who submits a treatment IND under this section is the sponsor-investigator for such IND and is responsible for meeting all applicable sponsor and investigator responsibilities under this part and 21 CFR parts 50 and 56.


§312.36 Emergency use of an investigational new drug.

Need for an investigational drug may arise in an emergency situation that does not allow time for submission of an IND in accordance with §312.23 or §312.34. In such a case, FDA may authorize shipment of the drug for a specified use in advance of submission of an IND. A request for such authorization may be transmitted to FDA by telephone or other rapid communication means. For investigational biological drugs, the request should be directed to the Division of Biological Investigational New Drugs (HFB-230), Center for Biologics Evaluation and Research, 8800 Rockville Pike, Bethesda, MD 20892, 301-443-4864. For all other investigational drugs, the request for authorization should be directed to the Document Management and Reporting Branch (HFD-53), Center for Drug Evaluation and Research, 5600 Fishers Lane, Rockville, MD 20857, 301-443-4320. After normal working hours, eastern standard time, the request should be directed to the FDA Division of Emergency and Epidemiological Operations, 202-857-8400. Except in extraordinary circumstances, such authorization will be conditioned on the sponsor making an appropriate IND submission as soon as practicable after receiving the authorization.


§312.38 Withdrawal of an IND.

(a) At any time a sponsor may withdraw an effective IND without prejudice.
(b) If an IND is withdrawn, FDA shall be so notified, all clinical investigations conducted under the IND shall be ended, all current investigators notified, and all stocks of the drug returned to the sponsor or otherwise disposed of at the request of the sponsor in accordance with §312.59.
(c) If an IND is withdrawn because of a safety reason, the sponsor shall promptly so inform FDA, all participating investigators, and all reviewing Institutional Review Boards, together with the reasons for such withdrawal.


Subpart C--Administrative Actions

§312.40 General requirements for use of an investigational new drug in a clinical investigation.

(a) An investigational new drug may be used in a clinical investigation if the following conditions are met:
   (1) The sponsor of the investigation submits an IND for the drug to FDA; the IND is in effect under paragraph (b) of this section; and the sponsor complies with all
applicable requirements in this part and parts 50 and 56 with respect to the conduct of the clinical investigations; and

(2) Each participating investigator conducts his or her investigation in compliance with the requirements of this part and parts 50 and 56.

(b) An IND goes into effect:

(1) Thirty days after FDA receives the IND, unless FDA notifies the sponsor that the investigations described in the IND are subject to a clinical hold under §312.42; or

(2) On earlier notification by FDA that the clinical investigations in the IND may begin. FDA will notify the sponsor in writing of the date it receives the IND.

(c) A sponsor may ship an investigational new drug to investigators named in the IND:

(1) Thirty days after FDA receives the IND; or

(2) On earlier FDA authorization to ship the drug.

(d) An investigator may not administer an investigational new drug to human subjects until the IND goes into effect under paragraph (b) of this section.

§312.41 Comment and advice on an IND.

(a) FDA may at any time during the course of the investigation communicate with the sponsor orally or in writing about deficiencies in the IND or about FDA's need for more data or information.

(b) On the sponsor's request, FDA will provide advice on specific matters relating to an IND. Examples of such advice may include advice on the adequacy of technical data to support an investigational plan, on the design of a clinical trial, and on whether proposed investigations are likely to produce the data and information that is needed to meet requirements for a marketing application.

(c) Unless the communication is accompanied by a clinical hold order under §312.42, FDA communications with a sponsor under this section are solely advisory and do not require any modification in the planned or ongoing clinical investigations or response to the agency.


§312.42 Clinical holds and requests for modification.

(a) General. A clinical hold is an order issued by FDA to the sponsor to delay a proposed clinical investigation or to suspend an ongoing investigation. The clinical hold order may apply to one or more of the investigations covered by an IND. When a proposed study is placed on clinical hold, subjects may not be given the investigational drug. When an ongoing study is placed on clinical hold, no new subjects may be recruited to the study and placed on the investigational drug; patients already in the study should be taken off therapy involving the investigational drug unless specifically permitted by FDA in the interest of patient safety.

(b) Grounds for imposition of clinical hold—

(1) Clinical hold of a Phase 1 study under an IND. FDA may place a proposed or ongoing Phase 1 investigation on clinical hold if it finds that:

(i) Human subjects are or would be exposed to an unreasonable and significant risk of illness or injury;
(ii) The clinical investigators named in the IND are not qualified by reason of their scientific training and experience to conduct the investigation described in the IND;

(iii) The investigator brochure is misleading, erroneous, or materially incomplete; or

(iv) The IND does not contain sufficient information required under §312.23 to assess the risks to subjects of the proposed studies.

(v) The IND is for the study of an investigational drug intended to treat a life-threatening disease or condition that affects both genders, and men or women with reproductive potential who have the disease or condition being studied are excluded from eligibility because of a risk or potential risk from use of the investigational drug of reproductive toxicity (i.e., affecting reproductive organs) or developmental toxicity (i.e., affecting potential offspring). The phrase “women with reproductive potential” does not include pregnant women. For purposes of this paragraph, “life-threatening illnesses or diseases” are defined as “diseases or conditions where the likelihood of death is high unless the course of the disease is interrupted.” The clinical hold would not apply under this paragraph to clinical studies conducted:

(A) Under special circumstances, such as studies pertinent only to one gender (e.g., studies evaluating the excretion of a drug in semen or the effects on menstrual function);

(B) Only in men or women, as long as a study that does not exclude members of the other gender with reproductive potential is being conducted concurrently, has been conducted, or will take place within a reasonable time agreed upon by the agency; or

(C) Only in subjects who do not suffer from the disease or condition for which the drug is being studied.

(2) Clinical hold of a Phase 2 or 3 study under an IND. FDA may place a proposed or ongoing Phase 2 or 3 investigation on clinical hold if it finds that:

(i) Any of the conditions in paragraphs (b)(1)(i) through (b)(1)(v) of this section apply; or

(ii) The plan or protocol for the investigation is clearly deficient in design to meet its stated objectives.

(3) Clinical hold of a treatment IND or treatment protocol.

(i) Proposed use. FDA may place a proposed treatment IND or treatment protocol on clinical hold if it is determined that:

(A) The pertinent criteria in §312.34(b) for permitting the treatment use to begin are not satisfied; or

(B) The treatment protocol or treatment IND does not contain the information required under §312.35 (a) or (b) to make the specified determination under §312.34(b).

(ii) Ongoing use. FDA may place an ongoing treatment protocol or treatment IND on clinical hold if it is determined that:
(A) There becomes available a comparable or satisfactory alternative drug or other therapy to treat that stage of the disease in the intended patient population for which the investigational drug is being used;

(B) The investigational drug is not under investigation in a controlled clinical trial under an IND in effect for the trial and not all controlled clinical trials necessary to support a marketing application have been completed, or a clinical study under the IND has been placed on clinical hold:

(C) The sponsor of the controlled clinical trial is not pursuing marketing approval with due diligence;

(D) If the treatment IND or treatment protocol is intended for a serious disease, there is insufficient evidence of safety and effectiveness to support such use; or

(E) If the treatment protocol or treatment IND was based on an immediately life-threatening disease, the available scientific evidence, taken as a whole, fails to provide a reasonable basis for concluding that the drug:

(1) May be effective for its intended use in its intended population; or

(2) Would not expose the patients to whom the drug is to be administered to an unreasonable and significant additional risk of illness or injury.

(iii) FDA may place a proposed or ongoing treatment IND or treatment protocol on clinical hold if it finds that any of the conditions in paragraph (b)(4)(i) through (b)(4)(viii) of this section apply.

(4) Clinical hold of any study that is not designed to be adequate and well-controlled.

FDA may place a proposed or ongoing investigation that is not designed to be adequate and well-controlled on clinical hold if it finds that:

(i) Any of the conditions in paragraph (b)(1) or (b)(2) of this section apply; or

(ii) There is reasonable evidence the investigation that is not designed to be adequate and well-controlled is impeding enrollment in, or otherwise interfering with the conduct or completion of, a study that is designed to be an adequate and well-controlled investigation of the same or another investigational drug; or

(iii) Insufficient quantities of the investigational drug exist to adequately conduct both the investigation that is not designed to be adequate and well-controlled and the investigations that are designed to be adequate and well-controlled; or

(iv) The drug has been studied in one or more adequate and well-controlled investigations that strongly suggest lack of effectiveness; or

(v) Another drug under investigation or approved for the same indication and available to the same patient population has demonstrated a better potential benefit/risk balance; or

(vi) The drug has received marketing approval for the same indication in the same patient population; or

(vii) The sponsor of the study that is designed to be an adequate and well-controlled investigation is not actively pursuing marketing approval of the investigational drug with due diligence; or
(viii) The Commissioner determines that it would not be in the public interest for the study to be conducted or continued. FDA ordinarily intends that clinical holds under paragraphs (b)(4)(ii), (b)(4)(iii) and (b)(4)(v) of this section would only apply to additional enrollment in nonconcurrently controlled trials rather than eliminating continued access to individuals already receiving the investigational drug.

(5) Clinical hold of any investigation involving an exception from informed consent under §50.24 of this chapter. FDA may place a proposed or ongoing investigation involving an exception from informed consent under §50.24 of this chapter on clinical hold if it is determined that:
   (i) Any of the conditions in paragraphs (b)(1) or (b)(2) of this section apply; or
   (ii) The pertinent criteria in §50.24 of this chapter for such an investigation to begin or continue are not submitted or not satisfied.

(6) Clinical hold of any investigation involving an exception from informed consent under §50.23(d) of this chapter. FDA may place a proposed or ongoing investigation involving an exception from informed consent under §50.23(d) of this chapter on clinical hold if it is determined that:
   (i) Any of the conditions in paragraphs (b)(1) or (b)(2) of this section apply; or
   (ii) A determination by the President to waive the prior consent requirement for the administration of an investigational new drug has not been made.

(c) Discussion of deficiency. Whenever FDA concludes that a deficiency exists in a clinical investigation that may be grounds for the imposition of clinical hold FDA will, unless patients are exposed to immediate and serious risk, attempt to discuss and satisfactorily resolve the matter with the sponsor before issuing the clinical hold order.

(d) Imposition of clinical hold. The clinical hold order may be made by telephone or other means of rapid communication or in writing. The clinical hold order will identify the studies under the IND to which the hold applies, and will briefly explain the basis for the action. The clinical hold order will be made by or on behalf of the Division Director with responsibility for review of the IND. As soon as possible, and no more than 30 days after imposition of the clinical hold, the Division Director will provide the sponsor a written explanation of the basis for the hold.

(e) Resumption of clinical investigations. An investigation may only resume after FDA (usually the Division Director, or the Director's designee, with responsibility for review of the IND) has notified the sponsor that the investigation may proceed. Resumption of the affected investigation(s) will be authorized when the sponsor corrects the deficiency(ies) previously cited or otherwise satisfies the agency that the investigation(s) can proceed. FDA may notify a sponsor of its determination regarding the clinical hold by telephone or other means of rapid communication. If a sponsor of an IND that has been placed on clinical hold requests in writing that the clinical hold be removed and submits a complete response to the issue(s) identified in the clinical hold order, FDA shall respond in writing to the sponsor within 30-calendar days of receipt of the request and the complete response. FDA's response will either remove or maintain the clinical hold, and will state the reasons for such determination. Notwithstanding the 30- calendar day response time, a sponsor may
not proceed with a clinical trial on which a clinical hold has been imposed until the
sponsor has been notified by FDA that the hold has been lifted.
(f) Appeal. If the sponsor disagrees with the reasons cited for the clinical hold, the
sponsor may request reconsideration of the decision in accordance with §312.48.
(g) Conversion of IND on clinical hold to inactive status. If all investigations covered by
an IND remain on clinical hold for 1 year or more, the IND may be placed on inactive
status by FDA under §312.45.

FR 51530, Oct. 2, 1996; 63 FR 68678, Dec. 14, 1998; 64 FR 54189, Oct. 5, 1999; 65 FR 34971, June 1,
2000]

§312.44 Termination.
(a) General. This section describes the procedures under which FDA may terminate an
IND. If an IND is terminated, the sponsor shall end all clinical investigations
conducted under the IND and recall or otherwise provide for the disposition of all
unused supplies of the drug. A termination action may be based on deficiencies in the
IND or in the conduct of an investigation under an IND. Except as provided in
paragraph (d) of this section, a termination shall be preceded by a proposal to
terminate by FDA and an opportunity for the sponsor to respond. FDA will, in
general, only initiate an action under this section after first attempting to resolve
differences informally or, when appropriate, through the clinical hold procedures
described in §312.42.
(b) Grounds for termination—
(1) Phase 1. FDA may propose to terminate an IND during Phase 1 if it finds that:
   (i) Human subjects would be exposed to an unreasonable and significant risk of
   illness or injury.
   (ii) The IND does not contain sufficient information required under §312.23 to
   assess the safety to subjects of the clinical investigations.
   (iii) The methods, facilities, and controls used for the manufacturing,
   processing, and packing of the investigational drug are inadequate to
   establish and maintain appropriate standards of identity, strength, quality,
   and purity as needed for subject safety.
   (iv) The clinical investigations are being conducted in a manner substantially
different than that described in the protocols submitted in the IND.
   (v) The drug is being promoted or distributed for commercial purposes not
   justified by the requirements of the investigation or permitted by §312.7.
   (vi) The IND, or any amendment or report to the IND, contains an untrue
   statement of a material fact or omits material information required by this
   part.
   (vii) The sponsor fails promptly to investigate and inform the Food and Drug
   Administration and all investigators of serious and unexpected adverse
   experiences in accordance with §312.32 or fails to make any other report
   required under this part.
   (viii) The sponsor fails to submit an accurate annual report of the investigations
   in accordance with §312.33.
(ix) The sponsor fails to comply with any other applicable requirement of this part, part 50, or part 56.
(x) The IND has remained on inactive status for 5 years or more.
(xi) The sponsor fails to delay a proposed investigation under the IND or to suspend an ongoing investigation that has been placed on clinical hold under §312.42(b)(4).

(2) Phase 2 or 3. FDA may propose to terminate an IND during Phase 2 or Phase 3 if FDA finds that:
(i) Any of the conditions in paragraphs (b)(1)(i) through (b)(1)(xi) of this section apply; or
(ii) The investigational plan or protocol(s) is not reasonable as a bona fide scientific plan to determine whether or not the drug is safe and effective for use; or
(iii) There is convincing evidence that the drug is not effective for the purpose for which it is being investigated.

(3) FDA may propose to terminate a treatment IND if it finds that:
(i) Any of the conditions in paragraphs (b)(1)(i) through (x) of this section apply; or
(ii) Any of the conditions in §312.42(b)(3) apply.

(c) Opportunity for sponsor response.
(1) If FDA proposes to terminate an IND, FDA will notify the sponsor in writing, and invite correction or explanation within a period of 30 days.

(2) On such notification, the sponsor may provide a written explanation or correction or may request a conference with FDA to provide the requested explanation or correction. If the sponsor does not respond to the notification within the allocated time, the IND shall be terminated.

(3) If the sponsor responds but FDA does not accept the explanation or correction submitted, FDA shall inform the sponsor in writing of the reason for the nonacceptance and provide the sponsor with an opportunity for a regulatory hearing before FDA under part 16 on the question of whether the IND should be terminated. The sponsor's request for a regulatory hearing must be made within 10 days of the sponsor's receipt of FDA's notification of nonacceptance.

(d) Immediate termination of IND. Notwithstanding paragraphs (a) through (c) of this section, if at any time FDA concludes that continuation of the investigation presents an immediate and substantial danger to the health of individuals, the agency shall immediately, by written notice to the sponsor from the Director of the Center for Drug Evaluation and Research or the Director of the Center for Biologics Evaluation and Research, terminate the IND. An IND so terminated is subject to reinstatement by the Director on the basis of additional submissions that eliminate such danger. If an IND is terminated under this paragraph, the agency will afford the sponsor an opportunity for a regulatory hearing under part 16 on the question of whether the IND should be reinstated.

§312.45 Inactive status.

(a) If no subjects are entered into clinical studies for a period of 2 years or more under an IND, or if all investigations under an IND remain on clinical hold for 1 year or more, the IND may be placed by FDA on inactive status. This action may be taken by FDA either on request of the sponsor or on FDA's own initiative. If FDA seeks to act on its own initiative under this section, it shall first notify the sponsor in writing of the proposed inactive status. Upon receipt of such notification, the sponsor shall have 30 days to respond as to why the IND should continue to remain active.

(b) If an IND is placed on inactive status, all investigators shall be so notified and all stocks of the drug shall be returned or otherwise disposed of in accordance with §312.59.

(c) A sponsor is not required to submit annual reports to an IND on inactive status. An inactive IND is, however, still in effect for purposes of the public disclosure of data and information under §312.130.

(d) A sponsor who intends to resume clinical investigation under an IND placed on inactive status shall submit a protocol amendment under §312.30 containing the proposed general investigational plan for the coming year and appropriate protocols. If the protocol amendment relies on information previously submitted, the plan shall reference such information. Additional information supporting the proposed investigation, if any, shall be submitted in an information amendment. Notwithstanding the provisions of §312.30, clinical investigations under an IND on inactive status may only resume

(1) 30 days after FDA receives the protocol amendment, unless FDA notifies the sponsor that the investigations described in the amendment are subject to a clinical hold under §312.42, or

(2) on earlier notification by FDA that the clinical investigations described in the protocol amendment may begin.

(e) An IND that remains on inactive status for 5 years or more may be terminated under §312.44.


§312.47 Meetings.

(a) General. Meetings between a sponsor and the agency are frequently useful in resolving questions and issues raised during the course of a clinical investigation. FDA encourages such meetings to the extent that they aid in the evaluation of the drug and in the solution of scientific problems concerning the drug, to the extent that FDA's resources permit. The general principle underlying the conduct of such meetings is that there should be free, full, and open communication about any scientific or medical question that may arise during the clinical investigation. These meetings shall be conducted and documented in accordance with part 10.

(b) “End-of-Phase 2” meetings and meetings held before submission of a marketing application. At specific times during the drug investigation process, meetings between FDA and a sponsor can be especially helpful in minimizing wasteful expenditures of time and money and thus in speeding the drug development and evaluation process. In particular, FDA has found that meetings at the end of Phase 2 of an investigation
(end-of-Phase 2 meetings) are of considerable assistance in planning later studies and that meetings held near completion of Phase 3 and before submission of a marketing application (“pre-NDA” meetings) are helpful in developing methods of presentation and submission of data in the marketing application that facilitate review and allow timely FDA response.

(1) End-of-Phase 2 meetings—

(i) Purpose. The purpose of an end-of-phase 2 meeting is to determine the safety of proceeding to Phase 3, to evaluate the Phase 3 plan and protocols and the adequacy of current studies and plans to assess pediatric safety and effectiveness, and to identify any additional information necessary to support a marketing application for the uses under investigation.

(ii) Eligibility for meeting. While the end-of-Phase 2 meeting is designed primarily for IND's involving new molecular entities or major new uses of marketed drugs, a sponsor of any IND may request and obtain an end-of-Phase 2 meeting.

(iii) Timing. To be most useful to the sponsor, end-of-Phase 2 meetings should be held before major commitments of effort and resources to specific Phase 3 tests are made. The scheduling of an end-of-Phase 2 meeting is not, however, intended to delay the transition of an investigation from Phase 2 to Phase 3.

(iv) Advance information. At least 1 month in advance of an end-of-Phase 2 meeting, the sponsor should submit background information on the sponsor's plan for Phase 3, including summaries of the Phase 1 and 2 investigations, the specific protocols for Phase 3 clinical studies, plans for any additional nonclinical studies, plans for pediatric studies, including a time line for protocol finalization, enrollment, completion, and data analysis, or information to support any planned request for waiver or deferral of pediatric studies, and, if available, tentative labeling for the drug. The recommended contents of such a submission are described more fully in FDA Staff Manual Guide 4850.7 that is publicly available under FDA's public information regulations in part 20.

(v) Conduct of meeting. Arrangements for an end-of-Phase 2 meeting are to be made with the division in FDA's Center for Drug Evaluation and Research or the Center for Biologics Evaluation and Research which is responsible for review of the IND. The meeting will be scheduled by FDA at a time convenient to both FDA and the sponsor. Both the sponsor and FDA may bring consultants to the meeting. The meeting should be directed primarily at establishing agreement between FDA and the sponsor of the overall plan for Phase 3 and the objectives and design of particular studies. The adequacy of the technical information to support Phase 3 studies and/or a marketing application may also be discussed. FDA will also provide its best judgment, at that time, of the pediatric studies that will be required for the drug product and whether their submission will be deferred until after approval. Agreements reached at the meeting on these matters will be recorded in minutes of the conference that will be taken by FDA in accordance with §10.65 and provided to the sponsor. The minutes along
with any other written material provided to the sponsor will serve as a permanent record of any agreements reached. Barring a significant scientific development that requires otherwise, studies conducted in accordance with the agreement shall be presumed to be sufficient in objective and design for the purpose of obtaining marketing approval for the drug.

(2) “Pre-NDA” and “pre-BLA” meetings. FDA has found that delays associated with the initial review of a marketing application may be reduced by exchanges of information about a proposed marketing application. The primary purpose of this kind of exchange is to uncover any major unresolved problems, to identify those studies that the sponsor is relying on as adequate and well-controlled to establish the drug's effectiveness, to identify the status of ongoing or needed studies adequate to assess pediatric safety and effectiveness, to acquaint FDA reviewers with the general information to be submitted in the marketing application (including technical information), to discuss appropriate methods for statistical analysis of the data, and to discuss the best approach to the presentation and formatting of data in the marketing application. Arrangements for such a meeting are to be initiated by the sponsor with the division responsible for review of the IND. To permit FDA to provide the sponsor with the most useful advice on preparing a marketing application, the sponsor should submit to FDA's reviewing division at least 1 month in advance of the meeting the following information:
(i) A brief summary of the clinical studies to be submitted in the application.
(ii) A proposed format for organizing the submission, including methods for presenting the data.
(iii) Information on the status of needed or ongoing pediatric studies.
(iv) Any other information for discussion at the meeting.


§312.48 Dispute resolution.

(a) General. The Food and Drug Administration is committed to resolving differences between sponsors and FDA reviewing divisions with respect to requirements for IND's as quickly and amicably as possible through the cooperative exchange of information and views.

(b) Administrative and procedural issues. When administrative or procedural disputes arise, the sponsor should first attempt to resolve the matter with the division in FDA's Center for Drug Evaluation and Research or Center for Biologics Evaluation and Research which is responsible for review of the IND, beginning with the consumer safety officer assigned to the application. If the dispute is not resolved, the sponsor may raise the matter with the person designated as ombudsman, whose function shall be to investigate what has happened and to facilitate a timely and equitable resolution. Appropriate issues to raise with the ombudsman include resolving difficulties in scheduling meetings and obtaining timely replies to inquiries. Further details on this procedure are contained in FDA Staff Manual Guide 4820.7 that is publicly available under FDA's public information regulations in part 20.
(c) Scientific and medical disputes.

(1) When scientific or medical disputes arise during the drug investigation process, sponsors should discuss the matter directly with the responsible reviewing officials. If necessary, sponsors may request a meeting with the appropriate reviewing officials and management representatives in order to seek a resolution. Requests for such meetings shall be directed to the director of the division in FDA's Center for Drug Evaluation and Research or Center for Biologics Evaluation and Research which is responsible for review of the IND. FDA will make every attempt to grant requests for meetings that involve important issues and that can be scheduled at mutually convenient times.

(2) The “end-of-Phase 2” and “pre-NDA” meetings described in §312.47(b) will also provide a timely forum for discussing and resolving scientific and medical issues on which the sponsor disagrees with the agency.

(3) In requesting a meeting designed to resolve a scientific or medical dispute, applicants may suggest that FDA seek the advice of outside experts, in which case FDA may, in its discretion, invite to the meeting one or more of its advisory committee members or other consultants, as designated by the agency. Applicants may rely on, and may bring to any meeting, their own consultants. For major scientific and medical policy issues not resolved by informal meetings, FDA may refer the matter to one of its standing advisory committees for its consideration and recommendations.


Subpart D--Responsibilities of Sponsors and Investigators

§312.50 General responsibilities of sponsors.

Sponsors are responsible for selecting qualified investigators, providing them with the information they need to conduct an investigation properly, ensuring proper monitoring of the investigation(s), ensuring that the investigation(s) is conducted in accordance with the general investigational plan and protocols contained in the IND, maintaining an effective IND with respect to the investigations, and ensuring that FDA and all participating investigators are promptly informed of significant new adverse effects or risks with respect to the drug. Additional specific responsibilities of sponsors are described elsewhere in this part.

§312.52 Transfer of obligations to a contract research organization.

(a) A sponsor may transfer responsibility for any or all of the obligations set forth in this part to a contract research organization. Any such transfer shall be described in writing. If not all obligations are transferred, the writing is required to describe each of the obligations being assumed by the contract research organization. If all obligations are transferred, a general statement that all obligations have been transferred is acceptable. Any obligation not covered by the written description shall be deemed not to have been transferred.

(b) A contract research organization that assumes any obligation of a sponsor shall comply with the specific regulations in this chapter applicable to this obligation and
shall be subject to the same regulatory action as a sponsor for failure to comply with any obligation assumed under these regulations. Thus, all references to “sponsor” in this part apply to a contract research organization to the extent that it assumes one or more obligations of the sponsor.

§312.53 Selecting investigators and monitors.
(a) Selecting investigators. A sponsor shall select only investigators qualified by training and experience as appropriate experts to investigate the drug.
(b) Control of drug. A sponsor shall ship investigational new drugs only to investigators participating in the investigation.
(c) Obtaining information from the investigator. Before permitting an investigator to begin participation in an investigation, the sponsor shall obtain the following:
   (1) A signed investigator statement (Form FDA-1572) containing:
      (i) The name and address of the investigator;
      (ii) The name and code number, if any, of the protocol(s) in the IND identifying the study(ies) to be conducted by the investigator;
      (iii) The name and address of any medical school, hospital, or other research facility where the clinical investigation(s) will be conducted;
      (iv) The name and address of any clinical laboratory facilities to be used in the study;
      (v) The name and address of the IRB that is responsible for review and approval of the study(ies);
      (vi) A commitment by the investigator that he or she:
         (a) Will conduct the study(ies) in accordance with the relevant, current protocol(s) and will only make changes in a protocol after notifying the sponsor, except when necessary to protect the safety, the rights, or welfare of subjects;
         (b) Will comply with all requirements regarding the obligations of clinical investigators and all other pertinent requirements in this part;
         (c) Will personally conduct or supervise the described investigation(s);
         (d) Will inform any potential subjects that the drugs are being used for investigational purposes and will ensure that the requirements relating to obtaining informed consent (21 CFR part 50) and institutional review board review and approval (21 CFR part 56) are met;
         (e) Will report to the sponsor adverse experiences that occur in the course of the investigation(s) in accordance with §312.64;
         (f) Has read and understands the information in the investigator's brochure, including the potential risks and side effects of the drug; and
         (g) Will ensure that all associates, colleagues, and employees assisting in the conduct of the study(ies) are informed about their obligations in meeting the above commitments.
   (vii) A commitment by the investigator that, for an investigation subject to an institutional review requirement under part 56, an IRB that complies with the requirements of that part will be responsible for the initial and continuing review and approval of the clinical investigation and that the investigator will promptly report to the IRB all changes in the research
activity and all unanticipated problems involving risks to human subjects or others, and will not make any changes in the research without IRB approval, except where necessary to eliminate apparent immediate hazards to the human subjects.

(viii) A list of the names of the subinvestigators (e.g., research fellows, residents) who will be assisting the investigator in the conduct of the investigation.

(2) Curriculum vitae. A curriculum vitae or other statement of qualifications of the investigator showing the education, training, and experience that qualifies the investigator as an expert in the clinical investigation of the drug for the use under investigation.

(3) Clinical protocol.
   (i) For Phase 1 investigations, a general outline of the planned investigation including the estimated duration of the study and the maximum number of subjects that will be involved.
   (ii) For Phase 2 or 3 investigations, an outline of the study protocol including an approximation of the number of subjects to be treated with the drug and the number to be employed as controls, if any; the clinical uses to be investigated; characteristics of subjects by age, sex, and condition; the kind of clinical observations and laboratory tests to be conducted; the estimated duration of the study; and copies or a description of case report forms to be used.

(4) Financial disclosure information. Sufficient accurate financial information to allow the sponsor to submit complete and accurate certification or disclosure statements required under part 54 of this chapter. The sponsor shall obtain a commitment from the clinical investigator to promptly update this information if any relevant changes occur during the course of the investigation and for 1 year following the completion of the study.

(d) Selecting monitors. A sponsor shall select a monitor qualified by training and experience to monitor the progress of the investigation.

§312.54 Emergency research under §50.24 of this chapter.

(a) The sponsor shall monitor the progress of all investigations involving an exception from informed consent under §50.24 of this chapter. When the sponsor receives from the IRB information concerning the public disclosures required by §50.24(a)(7)(ii) and (a)(7)(iii) of this chapter, the sponsor promptly shall submit to the IND file and to Docket Number 95S-0158 in the Dockets Management Branch (HFA-305), Food and Drug Administration, 12420 Parklawn Dr., rm. 1-23, Rockville, MD 20857, copies of the information that was disclosed, identified by the IND number.

(b) The sponsor also shall monitor such investigations to identify when an IRB determines that it cannot approve the research because it does not meet the criteria in the exception in §50.24(a) of this chapter or because of other relevant ethical concerns. The sponsor promptly shall provide this information in writing to FDA, investigators who are asked to participate in this or a substantially equivalent clinical
investigation, and other IRB's that are asked to review this or a substantially equivalent investigation.

[61 FR 51530, Oct. 2, 1996]

§312.55 Informing investigators.

(a) Before the investigation begins, a sponsor (other than a sponsor-investigator) shall give each participating clinical investigator an investigator brochure containing the information described in §312.23(a)(5).

(b) The sponsor shall, as the overall investigation proceeds, keep each participating investigator informed of new observations discovered by or reported to the sponsor on the drug, particularly with respect to adverse effects and safe use. Such information may be distributed to investigators by means of periodically revised investigator brochures, reprints or published studies, reports or letters to clinical investigators, or other appropriate means. Important safety information is required to be relayed to investigators in accordance with §312.32.


§312.56 Review of ongoing investigations.

(a) The sponsor shall monitor the progress of all clinical investigations being conducted under its IND.

(b) A sponsor who discovers that an investigator is not complying with the signed agreement (Form FDA-1572), the general investigational plan, or the requirements of this part or other applicable parts shall promptly either secure compliance or discontinue shipments of the investigational new drug to the investigator and end the investigator's participation in the investigation. If the investigator's participation in the investigation is ended, the sponsor shall require that the investigator dispose of or return the investigational drug in accordance with §312.59 and shall notify FDA.

(c) The sponsor shall review and evaluate the evidence relating to the safety and effectiveness of the drug as it is obtained from the investigator. The sponsors shall make such reports to FDA regarding information relevant to the safety of the drug as are required under §312.32. The sponsor shall make annual reports on the progress of the investigation in accordance with §312.33.

(d) A sponsor who determines that its investigational drug presents an unreasonable and significant risk to subjects shall discontinue those investigations that present the risk, notify FDA, all institutional review boards, and all investigators who have at any time participated in the investigation of the discontinuance, assure the disposition of all stocks of the drug outstanding as required by §312.59, and furnish FDA with a full report of the sponsor's actions. The sponsor shall discontinue the investigation as soon as possible, and in no event later than 5 working days after making the determination that the investigation should be discontinued. Upon request, FDA will confer with a sponsor on the need to discontinue an investigation.

§312.57 Recordkeeping and record retention.

(a) A sponsor shall maintain adequate records showing the receipt, shipment, or other disposition of the investigational drug. These records are required to include, as appropriate, the name of the investigator to whom the drug is shipped, and the date, quantity, and batch or code mark of each such shipment.

(b) A sponsor shall maintain complete and accurate records showing any financial interest in §54.4(a)(3)(i), (a)(3)(ii), (a)(3)(iii), and (a)(3)(iv) of this chapter paid to clinical investigators by the sponsor of the covered study. A sponsor shall also maintain complete and accurate records concerning all other financial interests of investigators subject to part 54 of this chapter.

(c) A sponsor shall retain the records and reports required by this part for 2 years after a marketing application is approved for the drug; or, if an application is not approved for the drug, until 2 years after shipment and delivery of the drug for investigational use is discontinued and FDA has been so notified.

(d) A sponsor shall retain reserve samples of any test article and reference standard identified in, and used in any of the bioequivalence or bioavailability studies described in, §320.38 or §320.63 of this chapter, and release the reserve samples to FDA upon request, in accordance with, and for the period specified in §320.38.


§312.58 Inspection of sponsor’s records and reports.

(a) FDA inspection. A sponsor shall upon request from any properly authorized officer or employee of the Food and Drug Administration, at reasonable times, permit such officer or employee to have access to and copy and verify any records and reports relating to a clinical investigation conducted under this part. Upon written request by FDA, the sponsor shall submit the records or reports (or copies of them) to FDA. The sponsor shall discontinue shipments of the drug to any investigator who has failed to maintain or make available records or reports of the investigation as required by this part.

(b) Controlled substances. If an investigational new drug is a substance listed in any schedule of the Controlled Substances Act (21 U.S.C. 801; 21 CFR part 1308), records concerning shipment, delivery, receipt, and disposition of the drug, which are required to be kept under this part or other applicable parts of this chapter shall, upon the request of a properly authorized employee of the Drug Enforcement Administration of the U.S. Department of Justice, be made available by the investigator or sponsor to whom the request is made, for inspection and copying. In addition, the sponsor shall assure that adequate precautions are taken, including storage of the investigational drug in a securely locked, substantially constructed cabinet, or other securely locked, substantially constructed enclosure, access to which is limited, to prevent theft or diversion of the substance into illegal channels of distribution.
§312.59 Disposition of unused supply of investigational drug.
The sponsor shall assure the return of all unused supplies of the investigational drug from each individual investigator whose participation in the investigation is discontinued or terminated. The sponsor may authorize alternative disposition of unused supplies of the investigational drug provided this alternative disposition does not expose humans to risks from the drug. The sponsor shall maintain written records of any disposition of the drug in accordance with §312.57.


§312.60 General responsibilities of investigators.
An investigator is responsible for ensuring that an investigation is conducted according to the signed investigator statement, the investigational plan, and applicable regulations; for protecting the rights, safety, and welfare of subjects under the investigator's care; and for the control of drugs under investigation. An investigator shall, in accordance with the provisions of part 50 of this chapter, obtain the informed consent of each human subject to whom the drug is administered, except as provided in §§50.23 or 50.24 of this chapter. Additional specific responsibilities of clinical investigators are set forth in this part and in parts 50 and 56 of this chapter.


§312.61 Control of the investigational drug.
An investigator shall administer the drug only to subjects under the investigator's personal supervision or under the supervision of a subinvestigator responsible to the investigator. The investigator shall not supply the investigational drug to any person not authorized under this part to receive it.

§312.62 Investigator recordkeeping and record retention.
(a) Disposition of drug. An investigator is required to maintain adequate records of the disposition of the drug, including dates, quantity, and use by subjects. If the investigation is terminated, suspended, discontinued, or completed, the investigator shall return the unused supplies of the drug to the sponsor, or otherwise provide for disposition of the unused supplies of the drug under §312.59.

(b) Case histories. An investigator is required to prepare and maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual administered the investigational drug or employed as a control in the investigation. Case histories include the case report forms and supporting data including, for example, signed and dated consent forms and medical records including, for example, progress notes of the physician, the individual's hospital chart(s), and the nurses' notes. The case history for each individual shall document that informed consent was obtained prior to participation in the study.

(c) Record retention. An investigator shall retain records required to be maintained under this part for a period of 2 years following the date a marketing application is approved for the drug for the indication for which it is being investigated; or, if no application
§312.64 Investigator reports.

(a) Progress reports. The investigator shall furnish all reports to the sponsor of the drug who is responsible for collecting and evaluating the results obtained. The sponsor is required under §312.33 to submit annual reports to FDA on the progress of the clinical investigations.

(b) Safety reports. An investigator shall promptly report to the sponsor any adverse effect that may reasonably be regarded as caused by, or probably caused by, the drug. If the adverse effect is alarming, the investigator shall report the adverse effect immediately.

(c) Final report. An investigator shall provide the sponsor with an adequate report shortly after completion of the investigator's participation in the investigation.

(d) Financial disclosure reports. The clinical investigator shall provide the sponsor with sufficient accurate financial information to allow an applicant to submit complete and accurate certification or disclosure statements as required under part 54 of this chapter. The clinical investigator shall promptly update this information if any relevant changes occur during the course of the investigation and for 1 year following the completion of the study.

§312.66 Assurance of IRB review.

An investigator shall assure that an IRB that complies with the requirements set forth in part 56 will be responsible for the initial and continuing review and approval of the proposed clinical study. The investigator shall also assure that he or she will promptly report to the IRB all changes in the research activity and all unanticipated problems involving risk to human subjects or others, and that he or she will not make any changes in the research without IRB approval, except where necessary to eliminate apparent immediate hazards to human subjects.

§312.68 Inspection of investigator's records and reports.

An investigator shall upon request from any properly authorized officer or employee of FDA, at reasonable times, permit such officer or employee to have access to, and copy and verify any records or reports made by the investigator pursuant to §312.62. The investigator is not required to divulge subject names unless the records of particular individuals require a more detailed study of the cases, or unless there is reason to believe that the records do not represent actual case studies, or do not represent actual results obtained.
§312.69 Handling of controlled substances.
If the investigational drug is subject to the Controlled Substances Act, the investigator shall take adequate precautions, including storage of the investigational drug in a securely locked, substantially constructed cabinet, or other securely locked, substantially constructed enclosure, access to which is limited, to prevent theft or diversion of the substance into illegal channels of distribution.

§312.70 Disqualification of a clinical investigator.
(a) If FDA has information indicating that an investigator (including a sponsor-investigator) has repeatedly or deliberately failed to comply with the requirements of this part, part 50, or part 56 of this chapter, or has submitted to FDA or to the sponsor false information in any required report, the Center for Drug Evaluation and Research or the Center for Biologics Evaluation and Research will furnish the investigator written notice of the matter complained of and offer the investigator an opportunity to explain the matter in writing, or, at the option of the investigator, in an informal conference. If an explanation is offered but not accepted by the Center for Drug Evaluation and Research or the Center for Biologics Evaluation and Research, the investigator will be given an opportunity for a regulatory hearing under part 16 on the question of whether the investigator is entitled to receive investigational new drugs.

(b) After evaluating all available information, including any explanation presented by the investigator, if the Commissioner determines that the investigator has repeatedly or deliberately failed to comply with the requirements of this part, part 50, or part 56 of this chapter, or has deliberately or repeatedly submitted false information to FDA or to the sponsor in any required report, the Commissioner will notify the investigator and the sponsor of any investigation in which the investigator has been named as a participant that the investigator is not entitled to receive investigational drugs. The notification will provide a statement of basis for such determination.

(c) Each IND and each approved application submitted under part 314 containing data reported by an investigator who has been determined to be ineligible to receive investigational drugs will be examined to determine whether the investigator has submitted unreliable data that are essential to the continuation of the investigation or essential to the approval of any marketing application.

(d) If the Commissioner determines, after the unreliable data submitted by the investigator are eliminated from consideration, that the data remaining are inadequate to support a conclusion that it is reasonably safe to continue the investigation, the Commissioner will notify the sponsor who shall have an opportunity for a regulatory hearing under part 16. If a danger to the public health exists, however, the Commissioner shall terminate the IND immediately and notify the sponsor of the determination. In such case, the sponsor shall have an opportunity for a regulatory hearing before FDA under part 16 on the question of whether the IND should be reinstated.

(e) If the Commissioner determines, after the unreliable data submitted by the investigator are eliminated from consideration, that the continued approval of the drug product for which the data were submitted cannot be justified, the Commissioner will proceed to withdraw approval of the drug product in accordance with the applicable provisions of the act.
(f) An investigator who has been determined to be ineligible to receive investigational drugs may be reinstated as eligible when the Commissioner determines that the investigator has presented adequate assurances that the investigator will employ investigational drugs solely in compliance with the provisions of this part and of parts 50 and 56.


Subpart E--Drugs Intended to Treat Life-threatening and Severely-debilitating Illnesses

§312.80 Purpose.


Source: 53 FR 41523, Oct. 21, 1988, unless otherwise noted.

The purpose of this section is to establish procedures designed to expedite the development, evaluation, and marketing of new therapies intended to treat persons with life-threatening and severely-debilitating illnesses, especially where no satisfactory alternative therapy exists. As stated §314.105(c) of this chapter, while the statutory standards of safety and effectiveness apply to all drugs, the many kinds of drugs that are subject to them, and the wide range of uses for those drugs, demand flexibility in applying the standards. The Food and Drug Administration (FDA) has determined that it is appropriate to exercise the broadest flexibility in applying the statutory standards, while preserving appropriate guarantees for safety and effectiveness. These procedures reflect the recognition that physicians and patients are generally willing to accept greater risks or side effects from products that treat life-threatening and severely-debilitating illnesses, than they would accept from products that treat less serious illnesses. These procedures also reflect the recognition that the benefits of the drug need to be evaluated in light of the severity of the disease being treated. The procedure outlined in this section should be interpreted consistent with that purpose.

§312.81 Scope.

This section applies to new drug and biological products that are being studied for their safety and effectiveness in treating life-threatening or severely-debilitating diseases.

(a) For purposes of this section, the term “life-threatening” means:

(1) Diseases or conditions where the likelihood of death is high unless the course of the disease is interrupted; and

(2) Diseases or conditions with potentially fatal outcomes, where the end point of clinical trial analysis is survival.

(b) For purposes of this section, the term “severely debilitating” means diseases or conditions that cause major irreversible morbidity.

(c) Sponsors are encouraged to consult with FDA on the applicability of these procedures to specific products.

[53 FR 41523, Oct. 21, 1988, as amended at 64 FR 401, Jan. 5, 1999]
§312.82 Early consultation.
For products intended to treat life-threatening or severely-debilitating illnesses, sponsors may request to meet with FDA-reviewing officials early in the drug development process to review and reach agreement on the design of necessary preclinical and clinical studies. Where appropriate, FDA will invite to such meetings one or more outside expert scientific consultants or advisory committee members. To the extent FDA resources permit, agency reviewing officials will honor requests for such meetings:
(a) Pre-investigational new drug (IND) meetings. Prior to the submission of the initial IND, the sponsor may request a meeting with FDA-reviewing officials. The primary purpose of this meeting is to review and reach agreement on the design of animal studies needed to initiate human testing. The meeting may also provide an opportunity for discussing the scope and design of phase 1 testing, plans for studying the drug product in pediatric populations, and the best approach for presentation and formatting of data in the IND.
(b) End-of-phase 1 meetings. When data from phase 1 clinical testing are available, the sponsor may again request a meeting with FDA-reviewing officials. The primary purpose of this meeting is to review and reach agreement on the design of phase 2 controlled clinical trials, with the goal that such testing will be adequate to provide sufficient data on the drug's safety and effectiveness to support a decision on its approvability for marketing, and to discuss the need for, as well as the design and timing of, studies of the drug in pediatric patients. For drugs for life-threatening diseases, FDA will provide its best judgment, at that time, whether pediatric studies will be required and whether their submission will be deferred until after approval. The procedures outlined in §312.47(b)(1) with respect to end-of-phase 2 conferences, including documentation of agreements reached, would also be used for end-of-phase 1 meetings.


§312.83 Treatment protocols.
If the preliminary analysis of phase 2 test results appears promising, FDA may ask the sponsor to submit a treatment protocol to be reviewed under the procedures and criteria listed in §§312.34 and 312.35. Such a treatment protocol, if requested and granted, would normally remain in effect while the complete data necessary for a marketing application are being assembled by the sponsor and reviewed by FDA (unless grounds exist for clinical hold of ongoing protocols, as provided in §312.42(b)(3)(ii)).

§312.84 Risk-benefit analysis in review of marketing applications for drugs to treat life-threatening and severely-debilitating illnesses.
(a) FDA's application of the statutory standards for marketing approval shall recognize the need for a medical risk-benefit judgment in making the final decision on approvability. As part of this evaluation, consistent with the statement of purpose in §312.80, FDA will consider whether the benefits of the drug outweigh the known and potential risks of the drug and the need to answer remaining questions about risks and benefits of the drug, taking into consideration the severity of the disease and the absence of satisfactory alternative therapy.
(b) In making decisions on whether to grant marketing approval for products that have been the subject of an end-of-phase 1 meeting under §312.82, FDA will usually seek the advice of outside expert scientific consultants or advisory committees. Upon the filing of such a marketing application under §314.101 or part 601 of this chapter, FDA will notify the members of the relevant standing advisory committee of the application's filing and its availability for review.

(c) If FDA concludes that the data presented are not sufficient for marketing approval, FDA will issue (for a drug) a not approvable letter pursuant to §314.120 of this chapter, or (for a biologic) a deficiencies letter consistent with the biological product licensing procedures. Such letter, in describing the deficiencies in the application, will address why the results of the research design agreed to under §312.82, or in subsequent meetings, have not provided sufficient evidence for marketing approval. Such letter will also describe any recommendations made by the advisory committee regarding the application.

(d) Marketing applications submitted under the procedures contained in this section will be subject to the requirements and procedures contained in part 314 or part 600 of this chapter, as well as those in this subpart.

§312.85 Phase 4 studies.
Concurrent with marketing approval, FDA may seek agreement from the sponsor to conduct certain postmarketing (phase 4) studies to delineate additional information about the drug's risks, benefits, and optimal use. These studies could include, but would not be limited to, studying different doses or schedules of administration than were used in phase 2 studies, use of the drug in other patient populations or other stages of the disease, or use of the drug over a longer period of time.

§312.86 Focused FDA regulatory research.
At the discretion of the agency, FDA may undertake focused regulatory research on critical rate-limiting aspects of the preclinical, chemical/manufacturing, and clinical phases of drug development and evaluation. When initiated, FDA will undertake such research efforts as a means for meeting a public health need in facilitating the development of therapies to treat life-threatening or severely debilitating illnesses.

§312.87 Active monitoring of conduct and evaluation of clinical trials.
For drugs covered under this section, the Commissioner and other agency officials will monitor the progress of the conduct and evaluation of clinical trials and be involved in facilitating their appropriate progress.

§312.88 Safeguards for patient safety.
All of the safeguards incorporated within parts 50, 56, 312, 314, and 600 of this chapter designed to ensure the safety of clinical testing and the safety of products following marketing approval apply to drugs covered by this section. This includes the requirements for informed consent (part 50 of this chapter) and institutional review boards (part 56 of this chapter). These safeguards further include the review of animal studies prior to initial human testing (§312.23), and the monitoring of adverse drug experiences through the requirements of IND safety reports (§312.32), safety update
reports during agency review of a marketing application (§314.50 of this chapter), and postmarketing adverse reaction reporting (§314.80 of this chapter).

Subpart F--Miscellaneous

§312.110 Import and export requirements.
(a) Imports. An investigational new drug offered for import into the United States complies with the requirements of this part if it is subject to an IND that is in effect for it under §312.40 and:
(1) The consignee in the United States is the sponsor of the IND;
(2) the consignee is a qualified investigator named in the IND; or
(3) the consignee is the domestic agent of a foreign sponsor, is responsible for the control and distribution of the investigational drug, and the IND identifies the consignee and describes what, if any, actions the consignee will take with respect to the investigational drug.
(b) Exports. An investigational new drug intended for export from the United States complies with the requirements of this part as follows:
(1) If an IND is in effect for the drug under §312.40 and each person who receives the drug is an investigator named in the application; or
(2) If FDA authorizes shipment of the drug for use in a clinical investigation. Authorization may be obtained as follows:
(i) Through submission to the International Affairs Staff (HFY-50), Associate Commissioner for Health Affairs, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, of a written request from the person that seeks to export the drug. A request must provide adequate information about the drug to satisfy FDA that the drug is appropriate for the proposed investigational use in humans, that the drug will be used for investigational purposes only, and that the drug may be legally used by that consignee in the importing country for the proposed investigational use. The request shall specify the quantity of the drug to be shipped per shipment and the frequency of expected shipments. If FDA authorizes exportation under this paragraph, the agency shall concurrently notify the government of the importing country of such authorization.
(ii) Through submission to the International Affairs Staff (HFY-50), Associate Commissioner for Health Affairs, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, of a formal request from an authorized official of the government of the country to which the drug is proposed to be shipped. A request must specify that the foreign government has adequate information about the drug and the proposed investigational use, that the drug will be used for investigational purposes only, and that the foreign government is satisfied that the drug may legally be used by the intended consignee in that country. Such a request shall specify the quantity of drug to be shipped per shipment and the frequency of expected shipments.
(iii) Authorization to export an investigational drug under paragraph (b)(2)(i) or (ii) of this section may be revoked by FDA if the agency finds that the conditions underlying its authorization are no longer met.

(3) This paragraph applies only where the drug is to be used for the purpose of clinical investigation.

(4) This paragraph does not apply to the export of new drugs (including biological products, antibiotic drugs, and insulin) approved or authorized for export under section 802 of the act (21 U.S.C. 382) or section 351(h)(1)(A) of the Public Health Service Act (42 U.S.C. 262(h)(1)(A)).


§312.120 Foreign clinical studies not conducted under an IND.

(a) Introduction. This section describes the criteria for acceptance by FDA of foreign clinical studies not conducted under an IND. In general, FDA accepts such studies provided they are well designed, well conducted, performed by qualified investigators, and conducted in accordance with ethical principles acceptable to the world community. Studies meeting these criteria may be utilized to support clinical investigations in the United States and/or marketing approval. Marketing approval of a new drug based solely on foreign clinical data is governed by §314.106.

(b) Data submissions. A sponsor who wishes to rely on a foreign clinical study to support an IND or to support an application for marketing approval shall submit to FDA the following information:

(1) A description of the investigator's qualifications;

(2) A description of the research facilities;

(3) A detailed summary of the protocol and results of the study, and, should FDA request, case records maintained by the investigator or additional background data such as hospital or other institutional records;

(4) A description of the drug substance and drug product used in the study, including a description of components, formulation, specifications, and bioavailability of the specific drug product used in the clinical study, if available; and

(5) If the study is intended to support the effectiveness of a drug product, information showing that the study is adequate and well controlled under §314.126.

(c) Conformance with ethical principles.

(1) Foreign clinical research is required to have been conducted in accordance with the ethical principles stated in the “Declaration of Helsinki” (see paragraph (c)(4) of this section) or the laws and regulations of the country in which the research was conducted, whichever represents the greater protection of the individual.

(2) For each foreign clinical study submitted under this section, the sponsor shall explain how the research conformed to the ethical principles contained in the “Declaration of Helsinki” or the foreign country's standards, whichever were used. If the foreign country's standards were used, the sponsor shall explain in detail how those standards differ from the “Declaration of Helsinki” and how they offer greater protection.
(3) When the research has been approved by an independent review committee, the sponsor shall submit to FDA documentation of such review and approval, including the names and qualifications of the members of the committee. In this regard, a “review committee” means a committee composed of scientists and, where practicable, individuals who are otherwise qualified (e.g., other health professionals or laymen). The investigator may not vote on any aspect of the review of his or her protocol by a review committee.

(4) The “Declaration of Helsinki” states as follows: Recommendations Guiding Physicians in Biomedical Research Involving Human Subjects

Introduction

It is the mission of the physician to safeguard the health of the people. His or her knowledge and conscience are dedicated to the fulfillment of this mission. The Declaration of Geneva of the World Medical Association binds the physician with the words, “The health of my patient will be my first consideration,” and the International Code of Medical Ethics declares that, “A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient.” The purpose of biomedical research involving human subjects must be to improve diagnostic, therapeutic and prophylactic procedures and the understanding of the aetiology and pathogenesis of disease. In current medical practice most diagnostic, therapeutic or prophylactic procedures involve hazards. This applies especially to biomedical research. Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects. In the field of biomedical research a fundamental distinction must be recognized between medical research in which the aim is essentially diagnostic or therapeutic for a patient, and medical research, the essential object of which is purely scientific and without implying direct diagnostic or therapeutic value to the person subjected to the research. Special caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected. Because it is essential that the results of laboratory experiments be applied to human beings to further scientific knowledge and to help suffering humanity, the World Medical Association has prepared the following recommendations as a guide to every physician in biomedical research involving human subjects. They should be kept under review in the future. It must be stressed that the standards as drafted are only a guide to physicians all over the world. Physicians are not relieved from criminal, civil and ethical responsibilities under the laws of their own countries.

I. Basic Principles

1. Biomedical research involving human subjects must conform to generally accepted scientific principles and should be based on adequately performed laboratory and animal experimentation and on a thorough knowledge of the scientific literature.

2. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol which should be transmitted for consideration, comment and guidance to a specially appointed committee independent of the
investigator and the sponsor provided that this independent committee
is in conformity with the laws and regulations of the country in
which the research experiment is performed.

3. Biomedical research involving human subjects should be conducted
only by scientifically qualified persons and under the supervision of a
clinically competent medical person. The responsibility for the human
subject must always rest with a medically qualified person and never
rest on the subject of the research, even though the subject has given
his or her consent.

4. Biomedical research involving human subjects cannot legitimately be
carried out unless the importance of the objective is in proportion to
the inherent risk to the subject.

5. Every biomedical research project involving human subjects should be
preceded by careful assessment of predictable risks in comparison with
foreseeable benefits to the subject or to others. Concern for the
interests of the subject must always prevail over the interests of
science and society.

6. The right of the research subject to safeguard his or her integrity must
always be respected. Every precaution should be taken to respect the
privacy of the subject and to minimize the impact of the study on the
subject's physical and mental integrity and on the personality of the
subject.

7. Physicians should abstain from engaging in research projects involving
human subjects unless they are satisfied that the hazards involved are
believed to be predictable. Physicians should cease any investigation if
the hazards are found to outweigh the potential benefits.

8. In publication of the results of his or her research, the physician is
obliged to preserve the accuracy of the results. Reports of
experimentation not in accordance with the principles laid down in this
Declaration should not be accepted for publication.

9. In any research on human beings, each potential subject must be
adequately informed of the aims, methods, anticipated benefits and
potential hazards of the study and the discomfort it may entail. He or
she should be informed that he or she is at liberty to abstain from
participation in the study and that he or she is free to withdraw his or
her consent to participation at any time. The physician should then
obtain the subject's freely-given informed consent, preferably in
writing.

10. When obtaining informed consent for the research project the
physician should be particularly cautious if the subject is in a
dependent relationship to him or her or may consent under duress. In
that case the informed consent should be obtained by a physician who
is not engaged in the investigation and who is completely independent
of this official relationship.

11. In case of legal incompetence, informed consent should be obtained
from the legal guardian in accordance with national legislation. Where
physical or mental incapacity makes it impossible to obtain informed
consent, or when the subject is a minor, permission from the
responsible relative replaces that of the subject in accordance with
national legislation. Whenever the minor child is in fact able to give a
consent, the minor's consent must be obtained in addition to the
consent of the minor's legal guardian.

12. The research protocol should always contain a statement of the ethical
considerations involved and should indicate that the principles
enunciated in the present Declaration are complied with.

II. Medical Research Combined with Professional Care (Clinical Research)

1. In the treatment of the sick person, the physician must be free to use a
new diagnostic and therapeutic measure, if in his or her judgment it
offers hope of saving life, reestablishing health or alleviating suffering.

2. The potential benefits, hazards and discomfort of a new method should
be weighed against the advantages of the best current diagnostic and
therapeutic methods.

3. In any medical study, every patient--including those of a control group,
if any--should be assured of the best proven diagnostic and therapeutic
method.

4. The refusal of the patient to participate in a study must never interfere
with the physician-patient relationship.

5. If the physician considers it essential not to obtain informed consent, the
specific reasons for this proposal should be stated in the experimental
protocol for transmission to the independent committee (I, 2).

6. The physician can combine medical research with professional care, the
objective being the acquisition of new medical knowledge, only to the
extent that medical research is justified by its potential diagnostic or
therapeutic value for the patient.

III. Non-Therapeutic Biomedical Research Involving Human Subjects (Non-
Clinical Biomedical Research)

1. In the purely scientific application of medical research carried out on a
human being, it is the duty of the physician to remain the protector of
the life and health of that person on whom biomedical research is
being carried out.

2. The subjects should be volunteers--either healthy persons or patients for
whom the experimental design is not related to the patient's illness.

3. The investigator or the investigating team should discontinue the
research if in his/her or their judgment it may, if continued, be harmful
to the individual.

4. In research on man, the interest of science and society should never take
precedence over considerations related to the well-being of the subject.

FR 401, Jan. 5, 1999; 67 FR 9586, Mar. 4, 2002]
§312.130 Availability for public disclosure of data and information in an IND.

(a) The existence of an investigational new drug application will not be disclosed by FDA unless it has previously been publicly disclosed or acknowledged.

(b) The availability for public disclosure of all data and information in an investigational new drug application for a new drug will be handled in accordance with the provisions established in §314.430 for the confidentiality of data and information in applications submitted in part 314. The availability for public disclosure of all data and information in an investigational new drug application for a biological product will be governed by the provisions of §§601.50 and 601.51.

(c) Notwithstanding the provisions of §314.430, FDA shall disclose upon request to an individual to whom an investigational new drug has been given a copy of any IND safety report relating to the use in the individual.

(d) The availability of information required to be publicly disclosed for investigations involving an exception from informed consent under §50.24 of this chapter will be handled as follows: Persons wishing to request the publicly disclosable information in the IND that was required to be filed in Docket Number 95S-0158 in the Dockets Management Branch (HFA-305), Food and Drug Administration, 12420 Parklawn Dr., rm. 1-23, Rockville, MD 20857, shall submit a request under the Freedom of Information Act.


§312.140 Address for correspondence.

(a) Except as provided in paragraph (b) of this section, a sponsor shall send an initial IND submission to the Central Document Room, Center for Drug Evaluation and Research, Food and Drug Administration, Park Bldg., Rm. 214, 12420 Parklawn Dr., Rockville, MD 20852. On receiving the IND, FDA will inform the sponsor which one of the divisions in the Center for Drug Evaluation and Research or the Center for Biologics Evaluation and Research is responsible for the IND. Amendments, reports, and other correspondence relating to matters covered by the IND should be directed to the appropriate division. The outside wrapper of each submission shall state what is contained in the submission, for example, “IND Application”, “Protocol Amendment”, etc.

(b) Applications for the products listed below should be submitted to the Division of Biological Investigational New Drugs (HFB-230), Center for Biologics Evaluation and Research, Food and Drug Administration, 8800 Rockville Pike, Bethesda, MD 20892.

(1) Products subject to the licensing provisions of the Public Health Service Act of July 1, 1944 (58 Stat. 682, as amended (42 U.S.C. 201 et seq.)) or subject to part 600;
(2) ingredients packaged together with containers intended for the collection, processing, or storage of blood or blood components;
(3) urokinase products;
(4) plasma volume expanders and hydroxyethyl starch for leukapheresis; and
(5) coupled antibodies, i.e., products that consist of an antibody component coupled with a drug or radionuclide component in which both components provide a pharmacological effect but the biological component determines the site of action.

(c) All correspondence relating to biological products for human use which are also radioactive drugs shall be submitted to the Division of Oncology and Radiopharmaceutical Drug Products (HFD-150), Center for Drug Evaluation and Research, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, except that applications for coupled antibodies shall be submitted in accordance with paragraph (b) of this section.

(d) All correspondence relating to export of an investigational drug under §312.110(b)(2) shall be submitted to the International Affairs Staff (HFY-50), Office of Health Affairs, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857.


§312.145 Guidance documents.

(a) FDA has made available guidance documents under §10.115 of this chapter to help you to comply with certain requirements of this part.

(b) The Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER) maintain lists of guidance documents that apply to the centers' regulations. The lists are maintained on the Internet and are published annually in the Federal Register. A request for a copy of the CDER list should be directed to the Office of Training and Communications, Division of Communications Management, Drug Information Branch (HFD-210), Center for Drug Evaluation and Research, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857. A request for a copy of the CBER list should be directed to the Office of Communication, Training, and Manufacturers Assistance (HFM-40), Center for Biologics Evaluation and Research, Food and Drug Administration, 1401 Rockville Pike, Rockville, MD 20852-1448.

[65 FR 56479, Sept. 19, 2000]

Subpart G--Drugs for Investigational Use in Laboratory Research Animals or In Vitro Tests

§312.160 Drugs for investigational use in laboratory research animals or in vitro tests.

(a) Authorization to ship.

(1) (i) A person may ship a drug intended solely for tests in vitro or in animals used only for laboratory research purposes if it is labeled as follows: CAUTION: Contains a new drug for investigational use only in laboratory research animals, or for tests in vitro. Not for use in humans.
(ii) A person may ship a biological product for investigational in vitro diagnostic use that is listed in §312.2(b)(2)(ii) if it is labeled as follows: CAUTION: Contains a biological product for investigational in vitro diagnostic tests only.

(2) A person shipping a drug under paragraph (a) of this section shall use due diligence to assure that the consignee is regularly engaged in conducting such tests and that the shipment of the new drug will actually be used for tests in vitro or in animals used only for laboratory research.

(3) A person who ships a drug under paragraph (a) of this section shall maintain adequate records showing the name and post office address of the expert to whom the drug is shipped and the date, quantity, and batch or code mark of each shipment and delivery. Records of shipments under paragraph (a)(1)(i) of this section are to be maintained for a period of 2 years after the shipment. Records and reports of data and shipments under paragraph (a)(1)(ii) of this section are to be maintained in accordance with §312.57(b). The person who ships the drug shall upon request from any properly authorized officer or employee of the Food and Drug Administration, at reasonable times, permit such officer or employee to have access to and copy and verify records required to be maintained under this section.

(b) Termination of authorization to ship. FDA may terminate authorization to ship a drug under this section if it finds that:

(1) The sponsor of the investigation has failed to comply with any of the conditions for shipment established under this section; or

(2) The continuance of the investigation is unsafe or otherwise contrary to the public interest or the drug is used for purposes other than bona fide scientific investigation. FDA will notify the person shipping the drug of its finding and invite immediate correction. If correction is not immediately made, the person shall have an opportunity for a regulatory hearing before FDA pursuant to part 16.

(c) Disposition of unused drug. The person who ships the drug under paragraph (a) of this section shall assure the return of all unused supplies of the drug from individual investigators whenever the investigation discontinues or the investigation is terminated. The person who ships the drug may authorize in writing alternative disposition of unused supplies of the drug provided this alternative disposition does not expose humans to risks from the drug, either directly or indirectly (e.g., through food-producing animals). The shipper shall maintain records of any alternative disposition.

21 CFR 314 APPLICATIONS FOR FDA APPROVAL TO MARKET A NEW DRUG

[Revised as of April 1, 2002]

Subpart A--General Provisions

§314.1 Scope of this part.
(a) This part sets forth procedures and requirements for the submission to, and the review by, the Food and Drug Administration of applications and abbreviated applications to market a new drug under section 505 of the Federal Food, Drug, and Cosmetic Act, as well as amendments, supplements, and postmarketing reports to them.
(b) This part does not apply to drug products subject to licensing by FDA under the Public Health Service Act (58 Stat. 632 as amended (42 U.S.C. 201 et seq.)) and subchapter F of chapter I of title 21 of the .
(c) References in this part to regulations in the Code of Federal Regulations are to chapter I of title 21, unless otherwise noted.

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

§314.3 Definitions.
(a) The definitions and interpretations contained in section 201 of the act apply to those terms when used in this part.
(b) The following definitions of terms apply to this part:
   Abbreviated application means the application described under §314.94, including all amendments and supplements to the application. “Abbreviated application” applies to both an abbreviated new drug application and an abbreviated antibiotic application.
   Act means the Federal Food, Drug, and Cosmetic Act (sections 201-901 (21 U.S.C. 301-392)).
   Applicant means any person who submits an application or abbreviated application or an amendment or supplement to them under this part to obtain FDA approval of a new drug or an antibiotic drug and any person who owns an approved application or abbreviated application.
   Application means the application described under §314.50, including all amendments and supplements to the application. 505(b)(2)
Application means an application submitted under section 505(b)(1) of the act for a
drug for which the investigations described in section 505(b)(1)(A) of the act
and relied upon by the applicant for approval of the application were not
conducted by or for the applicant and for which the applicant has not obtained a
right of reference or use from the person by or for whom the investigations were
conducted.

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

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

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

Drug substance means an active ingredient that is intended to furnish
pharmacological activity or other direct effect in the diagnosis, cure, mitigation,
treatment, or prevention of disease or to affect the structure or any function of
the human body, but does not include intermediates use in the synthesis of such
ingredient.

FDA means the Food and Drug Administration.

Listed drug means a new drug product that has an effective approval under section
505(c) of the act for safety and effectiveness or under section 505(j) of the act,
which has not been withdrawn or suspended under section 505(e)(1) through
(e)(5) or (j)(5) of the act, and which has not been withdrawn from sale for what
FDA has determined are reasons of safety or effectiveness. Listed drug status is
evidenced by the drug product's identification as a drug with an effective
approval in the current edition of FDA's “Approved Drug Products with
Therapeutic Equivalence Evaluations” (the list) or any current supplement
thereto, as a drug with an effective approval. A drug product is deemed to be a
listed drug on the date of effective approval of the application or abbreviated
application for that drug product.

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

Reference listed drug means the listed drug identified by FDA as the drug product
upon which an applicant relies in seeking approval of its abbreviated
application.

Right of reference or use means the authority to rely upon, and otherwise use, an
investigation for the purpose of obtaining approval of an application, including
the ability to make available the underlying raw data from the investigation for
FDA audit, if necessary.
The list means the list of drug products with effective approvals published in the current edition of FDA's publication “Approved Drug Products with Therapeutic Equivalence Evaluations” and any current supplement to the publication.

[50 FR 7493, Feb. 22, 1985, as amended at 57 FR 17981, Apr. 28, 1992]

Subpart B--Applications

§314.50 Content and format of an application.

Applications and supplements to approved applications are required to be submitted in the form and contain the information, as appropriate for the particular submission, required under this section. Three copies of the application are required: An archival copy, a review copy, and a field copy. An application for a new chemical entity will generally contain an application form, an index, a summary, five or six technical sections, case report tabulations of patient data, case report forms, drug samples, and labeling, including, if applicable, any Medication Guide required under part 208 of this chapter. Other applications will generally contain only some of those items, and information will be limited to that needed to support the particular submission. These include an application of the type described in section 505(b)(2) of the act, an amendment, and a supplement. The application is required to contain reports of all investigations of the drug product sponsored by the applicant, and all other information about the drug pertinent to an evaluation of the application that is received or otherwise obtained by the applicant from any source. FDA will maintain guidance documents on the format and content of applications to assist applicants in their preparation.

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

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

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

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

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

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

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

(c) Summary.

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

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

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

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

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

(iv) A summary of the chemistry, manufacturing, and controls section of the application.
(v) A summary of the nonclinical pharmacology and toxicology section of the application.

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

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

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

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

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

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

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

(ii) Drug product. A list of all components used in the manufacture of the drug product (regardless of whether they appear in the drug product); and a statement of the composition of the drug product; a statement of the specifications and analytical methods for each component; the name and address of each manufacturer the drug product; a description of the manufacturing and packaging procedures and in-process controls for the drug product; such specifications and analytical methods as are necessary to assure the identity, strength, quality, purity, and bioavailability of the drug product, including, for example, specifications relating to sterility, dissolution rate, containers and closure systems; and stability data with proposed expiration dating. The application may provide additionally for the use of alternatives to meet any of these requirements, including
alternative components, manufacturing and packaging procedures, in-process controls, methods, and specifications. Reference to the current edition of the U.S. Pharmacopeia and the National Formulary may satisfy relevant requirements in this paragraph.

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

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

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

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

(v) Except for a foreign applicant, the applicant shall include a statement certifying that the field copy of the application has been provided to the applicant's home FDA district office.

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

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

(ii) Studies of the toxicological effects of the drug as they relate to the drug's intended clinical uses, including, as appropriate, studies assessing the drug's acute, subacute, and chronic toxicity; carcinogenicity; and studies of toxicities related to the drug's particular mode of administration or conditions of use.

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

(iv) Any studies of the absorption, distribution, metabolism, and excretion of the drug in animals.
(v) For each nonclinical laboratory study subject to the good laboratory practice regulations under part 58 a statement that it was conducted in compliance with the good laboratory practice regulations in part 58, or, if the study was not conducted in compliance with those regulations, a brief statement of the reason for the noncompliance.

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

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

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

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

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

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

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

(iii) A description of any known mechanisms of resistance to the drug, including results of any known epidemiologic studies to demonstrate prevalence of resistance factors.

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

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

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

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

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

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

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

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

(a) The applicant shall submit an integrated summary of all available information about the safety of the drug product, including pertinent animal data, demonstrated or potential adverse effects of the drug, clinically significant drug/drug interactions, and other safety considerations, such as data from epidemiological studies of related drugs. The safety data shall be presented by gender, age, and racial subgroups. When appropriate, safety data from other subgroups of the population of patients treated also shall be presented, such as for patients with renal failure or patients with different levels of severity of the disease. A description of any statistical analyses performed in analyzing safety data should also be included, unless already included under paragraph (d)(5)(ii) of this section.

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

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

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

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

(x) If a sponsor has transferred any obligations for the conduct of any clinical study to a contract research organization, a statement containing the name and address of the contract research organization, identification of the clinical study, and a listing of the obligations transferred. If all obligations governing the conduct of the study have been transferred, a general statement of this transfer—in lieu of a listing of the specific obligations transferred—may be submitted.

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

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

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

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

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

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

(a) The drug product proposed for marketing;
(b) The drug substance used in the drug product from which the samples of the drug product were taken; and
(c) Reference standards and blanks (except that reference standards recognized in an official compendium need not be submitted).

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

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

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

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

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

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

(2) Case report forms. The application is required to contain copies of individual case report forms for each patient who died during a clinical study or who did not complete the study because of an adverse event, whether believed to be drug related or not, including patients receiving reference drugs or placebo. This requirement may be waived by FDA for specific studies if the case report forms are unnecessary for a proper review of the study.

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

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

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

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

(2) The applicant shall submit an accurate and complete English translation of each part of the application that is not in English. The applicant shall submit a copy of each original literature publication for which an English translation is submitted.
(3) If an applicant who submits a new drug application under section 505(b) of the act obtains a “right of reference or use,” as defined under §314.3(b), to an investigation described in clause (A) of section 505(b)(1) of the act, the applicant shall include in its application a written statement signed by the owner of the data from each such investigation that the applicant may rely on in support of the approval of its application, and provide FDA access to, the underlying raw data that provide the basis for the report of the investigation submitted in its application.

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

(i) Patent certification--
(1) Contents. A 505(b)(2) application is required to contain the following:
   (i) Patents claiming drug, drug product, or method of use.
      (A) Except as provided in paragraph (i)(2) 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 a drug (the drug product or drug substance that is a component of the drug product) on which investigations that are relied upon by the applicant for approval of its application were conducted or that claims an approved use for such drug and for which information is required to be filed under section 505(b) and (c) of the act 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 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 §314.52(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 drug product which is claimed by the patent or a use of which is claimed by the patent and with the requirements under §314.52(c) with respect to the content of the notice.
(B) If the drug on which investigations that are relied upon by the applicant were conducted is itself a licensed generic drug of a patented drug first approved under section 505(b) of the act, the appropriate patent certification under this section with respect to each patent that claims the first-approved patented drug or that claims an approved use for such a drug.

(ii) No relevant patents. If, in the opinion of the applicant and to the best of its knowledge, there are no patents described in paragraph (i)(1)(i) of this section, a certification in the following form: In the opinion and to the best knowledge of (name of applicant), there are no patents that claim the drug or drugs on which investigations that are relied upon in this application were conducted or that claim a use of such drug or drugs.

(iii) Method of use patent.

(A) If information that is submitted under section 505(b) or (c) of the act and §314.53 is for a method of use patent, 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, the applicant shall submit an applicable certification under paragraph (i)(1)(i) of this section.

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

(3) Licensing agreements. If a 505(b)(2) 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, the applicant shall submit a certification under paragraph (i)(1)(i)(A)(4) of this section (“Paragraph IV Certification”) as to that patent and a statement that it has been granted a patent license. If the patent owner consents to an immediate effective date upon approval of the 505(b)(2) application, the application shall contain a written statement from the patent owner that it has a licensing agreement with the applicant and that it consents to an immediate effective date.

(4) Late submission of patent information. If a patent described in paragraph (i)(1)(i)(A) of this section is issued and the holder of the approved application for the patented drug does not submit the required information on the patent within 30 days of issuance of the patent, an applicant who submitted a 505(b)(2) application that, before the submission of the patent information, contained an appropriate patent certification is not required to submit an amended certification. An applicant whose 505(b)(2) application is filed after a late submission of patent information or whose 505(b)(2) application was previously filed but did not contain an appropriate patent certification at the time of the
patent submission shall submit a certification under paragraph (i)(1)(i) or (i)(1)(ii) of this section or a statement under paragraph (i)(1)(iii) of this section as to that patent.

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

(6) Amended certifications. A certification submitted under paragraphs (i)(1)(i) through (i)(1)(iii) of this section may be amended at any time before the effective date of the approval of the application. An applicant shall submit an amended certification as an amendment to a pending application or by letter to an approved application. 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. Once an amendment or letter for the change in certification has been submitted, the application will no longer be considered to be one containing the prior certification.

(i) After finding of infringement. An applicant who has submitted a certification under paragraph (i)(1)(i)(A)(4) of this section and is sued for patent infringement within 45 days of the receipt of notice sent under §314.52 shall amend the certification if a final judgment in the action is entered finding the patent to be infringed unless the final judgment also finds the patent to be invalid. In the amended certification, the applicant shall certify under paragraph (i)(1)(i)(A)(3) of this section that the patent will expire on a specific date.

(ii) 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 (i)(1)(ii) of this section that no patents described in paragraph (i)(1)(i) of this section claim the drug or, if other relevant patents claim the drug, shall amend the certification to refer only to those relevant patents. In the amendment, the applicant shall 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 as an amendment to a pending application. Once an amendment for the change has been submitted, the application will no longer be considered to be one containing a certification under paragraph (i)(1)(i)(A)(4) of this section.

(iii) Other amendments.
(A) Except as provided in paragraphs (i)(4) and (i)(6)(iii)(B) 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.

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

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

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

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

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

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

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

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

(iii) “Conducted or sponsored by.” If the applicant was the sponsor named in the Form FDA-1571 for an investigational new drug application (IND) under which the new clinical investigation(s) that is essential to the approval of its application was conducted, identification of the IND by number. If the applicant was not the sponsor of the IND under which the clinical investigation(s) was conducted, a certification that the applicant or its predecessor in interest provided substantial support for the clinical investigation(s) that is essential to the approval of its application, and information supporting the certification. To demonstrate “substantial support,” an applicant must either provide a certified statement from a
certified public accountant that the applicant provided 50 percent or more of the cost of conducting the study or provide an explanation of why FDA should consider the applicant to have conducted or sponsored the study if the applicant's financial contribution to the study is less than 50 percent or the applicant did not sponsor the investigational new drug. A predecessor in interest is an entity, e.g., a corporation, that the applicant has taken over, merged with, or purchased, or from which the applicant has purchased all rights to the drug. Purchase of nonexclusive rights to a clinical investigation after it is completed is not sufficient to satisfy this definition.

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

(l) Format of an original application.

(1) The applicant shall submit a complete archival copy of the application that contains the information required under paragraphs (a) through (f) of this section. FDA will maintain the archival copy during the review of the application to permit individual reviewers to refer to information that is not contained in their particular technical sections of the application, to give other agency personnel access to the application for official business, and to maintain in one place a complete copy of the application. An applicant may submit on microfiche the portions of the archival copy of the application described in paragraphs (b) through (d) of this section. Information relating to samples and labeling (including, if applicable, any Medication Guide required under part 208 of this chapter), described in paragraph (e) of this section, is required to be submitted in hard copy. Tabulations of patient data and case report forms, described in paragraph (f) of this section, may be submitted on microfiche only if the applicant and FDA agree. If FDA agrees, the applicant may use another suitable microform system.

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

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

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

§314.52 Notice of certification of invalidity or noninfringement of a patent.

(a) Notice of certification. For each patent which claims the drug or drugs on which investigations that are relied upon by the applicant for approval of its application were conducted or which claims a use for such drug or drugs and which the applicant certifies under §314.50(i)(1)(i)(A)(4) that a patent 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 that is the subject of the certification or the representative designated by the owner to receive the notice. The name and address of the patent owner or its representative may be obtained from the United States Patent and Trademark Office; and

2. The holder of the approved application under section 505(b) of the act for each drug product which is claimed by the patent or a use of which is claimed by the patent and for which the applicant is seeking approval, or, if the application 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 application has been filed. At the same time, the applicant shall amend its 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 requirement under paragraph (c) of this section.

(c) Content of a notice. In the notice, the applicant shall cite section 505(b)(3)(B) of the act and shall include, but not be limited to, the following information:

1. A statement that a 505(b)(2) application submitted by the applicant has been filed by FDA.

2. The 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 agent in the United States authorized to accept service of process for the applicant.

(d) Amendment to an application. If an application is amended to include the certification described in §314.50(i), the applicant shall send the notice required by paragraph (a) of this section at the same time that the amendment to the application is submitted to FDA.

(e) Documentation of receipt of notice. The applicant shall amend its application to document receipt of the notice required under paragraph (a) of this section by each person provided the notice. The applicant shall include a copy of the return receipt or other similar evidence of the date the notification was received. FDA will accept as adequate documentation of the date of receipt a return receipt or a letter acknowledging receipt by the person provided the notice. An applicant may rely on another form of documentation only if FDA has agreed to such documentation in advance. A copy of the notice itself need not be submitted to the agency.

(f) Approval. If the requirements of this section are met, the agency will presume the notice to be complete and sufficient, and it will count the day following the date of receipt of the notice by the patent owner or its representative and by the approved application holder as the first day of the 45-day period provided for in section 505(c)(3)(C) of the act. FDA may, if the applicant amends its application with a written statement that a later date should be used, count from such later date.

[59 FR 50362, Oct. 3, 1994]

§314.53 Submission of patent information.

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

(b) Patents for which information must be submitted. An applicant described in paragraph (a) of this section shall submit information on each patent that claims the drug or a method of using the drug that is the subject of the new drug application or amendment or supplement to it and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product. For purposes of this part, such patents consist of drug substance (ingredient) patents, drug product (formulation and composition) patents, and method of use patents. Process patents are not covered by this section and information on process patents may not be submitted to FDA. For patents that claim a drug substance or drug product, the applicant shall submit information only on those patents that claim a drug product that is the subject of a pending or approved application, or that claim a drug substance that is a component of such a product. For patents that claim a method of use, the applicant
shall submit information only on those patents that claim indications or other conditions of use of a pending or approved application.

(c) Reporting requirements—
(1) General requirements. An applicant described in paragraph (a) of this section shall submit the following information for each patent described in paragraph (b) of this section:
   (i) Patent number and the date on which the patent will expire.
   (ii) Type of patent, i.e., drug, drug product, or method of use.
   (iii) Name of the patent owner.
   (iv) If the patent owner or applicant does not reside or have a place of business within the United States, the name of an agent (representative) of the patent owner or applicant who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the act and §§314.52 and 314.95.

(2) Formulation, composition, or method of use patents—
   (i) Original declaration. For each formulation, composition, or method of use patent, in addition to the patent information described in paragraph (c)(1) of this section the applicant shall submit the following declaration: The undersigned declares that Patent No. __________ covers the formulation, composition, and/or method of use of (name of drug product). This product is (currently approved under section 505 of the Federal Food, Drug, and Cosmetic Act) [or] (the subject of this application for which approval is being sought):

   (ii) Amendment of patent information upon approval. Within 30 days after the date of approval of its application, if the application contained a declaration required under paragraph (c)(2)(i) of this section, the applicant shall by letter amend the declaration to identify each patent that claims the formulation, composition, or the specific indications or other conditions of use that have been approved.

(3) No relevant patents. If the applicant believes that there are no patents which claim the drug or the drug product or which claim a method of using the drug product and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product, it shall so declare.

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

(d) When and where to submit patent information—
(1) Original application. An applicant shall submit with its original application submitted under this part, including an application described in section 505(b)(2) of the act, the information described in paragraph (c) of this section on each drug (ingredient), drug product (formulation and composition), and method of use patent issued before the application is filed with FDA and for which patent information is required to be submitted under this section. If a
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patent is issued after the application is filed with FDA but before the application is approved, the applicant shall, within 30 days of the date of issuance of the patent, submit the required patent information in an amendment to the application under §314.60.

(2) Supplements.

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

(A) To change the formulation;
(B) To add a new indication or other condition of use, including a change in route of administration;
(C) To change the strength;
(D) To make any other patented change regarding the drug, drug product, or any method of use.

(ii) If the applicant submits a supplement for one of the changes listed under paragraph (d)(2)(i) of this section and existing patents for which information has already been submitted to FDA claim the changed product, the applicant shall submit a certification with the supplement identifying the patents that claim the changed product.

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

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

(3) Patent information deadline. If a patent is issued for a drug, drug product, or method of use after an application is approved, the applicant shall submit to FDA the required patent information within 30 days of the date of issuance of the patent.

(4) Copies. The applicant shall submit two copies of each submission of patent information, an archival copy and a copy for the chemistry, manufacturing, and controls section of the review copy, to the Central Document Room, Center for Drug Evaluation and Research, Food and Drug Administration, Park Bldg., rm. 2-14, 12420 Parklawn Dr., Rockville, MD 20857. The applicant shall submit the patent information by letter separate from, but at the same time as, submission of the supplement.

(5) Submission date. Patent information shall be considered to be submitted to FDA as of the date the information is received by the Central Document Room.

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

(e) Public disclosure of patent information. FDA will publish in the list the patent number and expiration date of each patent that is required to be, and is, submitted to FDA by an applicant, and for each use patent, the approved indications or other conditions of use covered by a patent. FDA will publish such patent information upon approval of
the application, or, if the patent information is submitted by the applicant after approval of an application as provided under paragraph (d)(2) of this section, as soon as possible after the submission to the agency of the patent information. Patent information submitted by the last working day of a month will be published in that month's supplement to the list. Patent information received by the agency between monthly publication of supplements to the list will be placed on public display in FDA's Freedom of Information Staff. A request for copies of the file shall be sent in writing to the Freedom of Information Staff (HFI-35), Food and Drug Administration, rm. 12A-16, 5600 Fishers Lane, Rockville, MD 20857.

(f) Correction of patent information errors. If any person disputes the accuracy or relevance of patent information submitted to the agency under this section and published by FDA in the list, or believes that an applicant has failed to submit required patent information, that person must first notify the agency in writing stating the grounds for disagreement. Such notification should be directed to the Drug Information Services Branch (HFD-84), Center for Drug Evaluation and Research, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857. The agency will then request of the applicable new drug application holder that the correctness of the patent information or omission of patent information be confirmed. Unless the application holder withdraws or amends its patent information in response to FDA's request, the agency will not change the patent information in the list. If the new drug application holder does not change the patent information submitted to FDA, a 505(b)(2) application or an abbreviated new drug application under section 505(j) of the act submitted for a drug that is claimed by a patent for which information has been submitted must, despite any disagreement as to the correctness of the patent information, contain an appropriate certification for each listed patent.

[59 FR 50363, Oct. 3, 1994]

§314.54 Procedure for submission of an application requiring investigations for approval of a new indication for, or other change from, a listed drug.

(a) The act does not permit approval of an abbreviated new drug application for a new indication, nor does it permit approval of other changes in a listed drug if investigations, other than bioavailability or bioequivalence studies, are essential to the approval of the change. Any person seeking approval of a drug product that represents a modification of a listed drug (e.g., a new indication or new dosage form) and for which investigations, other than bioavailability or bioequivalence studies, are essential to the approval of the changes may, except as provided in paragraph (b) of this section, submit a 505(b)(2) application. This application need contain only that information needed to support the modification(s) of the listed drug.

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

(i) The information required under §314.50(a), (b), (c), (d)(1), (d)(3), (e), and (g), except that §314.50(d)(1)(ii)(c) shall contain the proposed or actual master production record, including a description of the equipment, to be used for the manufacture of a commercial lot of the drug product.
(ii) The information required under §314.50 (d)(2), (d)(4) (if an anti-infective drug), (d)(5), (d)(6), and (f) as needed to support the safety and effectiveness of the drug product.

(iii) Identification of the listed drug for which FDA has made a finding of safety and effectiveness and on which finding the applicant relies in seeking approval of its proposed drug product by established name, if any, proprietary name, dosage form, strength, route of administration, name of listed drug's application holder, and listed drug's approved application number.

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

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

(vi) Any patent certification or statement required under section 505(b)(2) of the act with respect to any relevant patents that claim the listed drug or that claim any other drugs on which investigations relied on by the applicant for approval of the application were conducted, or that claim a use for the listed or other drug.

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

(2) The applicant shall submit a review copy that contains the technical sections described in §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, and paragraph (d)(3), and the technical sections described in paragraphs (d)(2), (d)(4), (d)(5), (d)(6), and (f) when needed to support the modification. Each of the technical sections in the review copy is required to be separately bound with a copy of the information required under §314.50 (a), (b), and (c) and a copy of the proposed labeling.

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

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

(b) An application may not be submitted under this section for a drug product whose only difference from the reference listed drug is that:
(1) The extent to which its active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug; or
(2) The rate at which its active ingredient(s) is absorbed or otherwise made available to the site of action is unintentionally less than that of the reference listed drug.


§314.55 Pediatric use information.

(a) Required assessment. Except as provided in paragraphs (b), (c), and (d) of this section, each application for a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration shall contain data that are adequate to assess the safety and effectiveness of the drug product for the claimed indications in all relevant pediatric subpopulations, and to support dosing and administration for each pediatric subpopulation for which the drug is safe and effective. Where the course of the disease and the effects of the drug are sufficiently similar in adults and pediatric patients, FDA may conclude that pediatric effectiveness can be extrapolated from adequate and well-controlled studies in adults usually supplemented with other information obtained in pediatric patients, such as pharmacokinetic studies. Studies may not be needed in each pediatric age group, if data from one age group can be extrapolated to another. Assessments of safety and effectiveness required under this section for a drug product that represents a meaningful therapeutic benefit over existing treatments for pediatric patients must be carried out using appropriate formulations for each age group(s) for which the assessment is required.

(b) Deferred submission.

(1) FDA may, on its own initiative or at the request of an applicant, defer submission of some or all assessments of safety and effectiveness described in paragraph (a) of this section until after approval of the drug product for use in adults. Deferral may be granted if, among other reasons, the drug is ready for approval in adults before studies in pediatric patients are complete, or pediatric studies should be delayed until additional safety or effectiveness data have been collected. If an applicant requests deferred submission, the request must provide a certification from the applicant of the grounds for delaying pediatric studies, a description of the planned or ongoing studies, and evidence that the studies are being or will be conducted with due diligence and at the earliest possible time.

(2) If FDA determines that there is an adequate justification for temporarily delaying the submission of assessments of pediatric safety and effectiveness, the drug product may be approved for use in adults subject to the requirement that the applicant submit the required assessments within a specified time.

(c) Waivers—

(1) General. FDA may grant a full or partial waiver of the requirements of paragraph (a) of this section on its own initiative or at the request of an applicant. A request for a waiver must provide an adequate justification.

(2) Full waiver. An applicant may request a waiver of the requirements of paragraph (a) of this section if the applicant certifies that:
(i) The drug product does not represent a meaningful therapeutic benefit over existing treatments for pediatric patients and is not likely to be used in a substantial number of pediatric patients;

(ii) Necessary studies are impossible or highly impractical because, e.g., the number of such patients is so small or geographically dispersed; or

(iii) There is evidence strongly suggesting that the drug product would be ineffective or unsafe in all pediatric age groups.

(3) Partial waiver. An applicant may request a waiver of the requirements of paragraph (a) of this section with respect to a specified pediatric age group, if the applicant certifies that:

(i) The drug product does not represent a meaningful therapeutic benefit over existing treatments for pediatric patients in that age group, and is not likely to be used in a substantial number of patients in that age group;

(ii) Necessary studies are impossible or highly impractical because, e.g., the number of patients in that age group is so small or geographically dispersed;

(iii) There is evidence strongly suggesting that the drug product would be ineffective or unsafe in that age group; or

(iv) The applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for that age group have failed.

(4) FDA action on waiver. FDA shall grant a full or partial waiver, as appropriate, if the agency finds that there is a reasonable basis on which to conclude that one or more of the grounds for waiver specified in paragraphs (c)(2) or (c)(3) of this section have been met. If a waiver is granted on the ground that it is not possible to develop a pediatric formulation, the waiver will cover only those pediatric age groups requiring that formulation. If a waiver is granted because there is evidence that the product would be ineffective or unsafe in pediatric populations, this information will be included in the product's labeling.

(5) Definition of “meaningful therapeutic benefit”. For purposes of this section and §201.23 of this chapter, a drug will be considered to offer a meaningful therapeutic benefit over existing therapies if FDA estimates that:

(i) If approved, the drug would represent a significant improvement in the treatment, diagnosis, or prevention of a disease, compared to marketed products adequately labeled for that use in the relevant pediatric population. Examples of how improvement might be demonstrated include, for example, evidence of increased effectiveness in treatment, prevention, or diagnosis of disease, elimination or substantial reduction of a treatment-limiting drug reaction, documented enhancement of compliance, or evidence of safety and effectiveness in a new subpopulation; or

(ii) The drug is in a class of drugs or for an indication for which there is a need for additional therapeutic options.

(d) Exemption for orphan drugs. This section does not apply to any drug for an indication or indications for which orphan designation has been granted under part 316, subpart C, of this chapter.

[63 FR 66670, Dec. 2, 1998]
§314.60 Amendments to an unapproved application.

(a) Except as provided in paragraph (b) of this section, the applicant may submit an amendment to an application that is filed under §314.100, but not yet approved. The submission of a major amendment (for example, an amendment that contains significant new data from a previously unreported study or detailed new analyses of previously submitted data), whether on the applicant's own initiative or at the invitation of the agency, constitutes an agreement by the applicant under section 505(c) of the act to extend the date by which the agency is required to reach a decision on the application. Ordinarily, the agency will extend the review period for a major amendment but only for the time necessary to review the new information. However, the agency may not extend the review period more than 180 days. If the agency extends the review period for the application, the director of the division responsible for reviewing the application will notify the applicant of the length of the extension. The submission of an amendment that is not a major amendment will not extend the review period. An amendment that contains new clinical data from a previously unreported study shall contain a financial certification or disclosure statement or both as required by part 54 of this chapter, or FDA may refuse to accept any such amendment.

(b)

(1) An unapproved application may not be amended if all of the following conditions apply:

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

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

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

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

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

(c) The applicant shall submit a field copy of each amendment to §314.50(d)(1). The applicant, other than a foreign applicant, shall include in its submission of each such amendment to FDA a statement certifying that a field copy of the amendment has been sent to the applicant's home FDA district office.

§314.65 Withdrawal by the applicant of an unapproved application.

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

§314.70 Supplements and other changes to an approved application.

(a) Changes to an approved application. The applicant shall notify FDA about each change in each condition established in an approved application beyond the variations already provided for in the application. The notice is required to describe the change fully. Depending on the type of change, the applicant shall notify FDA about it in a supplemental application under paragraph (b) or (c) of this section or by inclusion of the information in the annual report to the application under paragraph (d) of this section. Notwithstanding the requirements of paragraphs (b) and (c) of this section, an applicant shall make a change provided for in those paragraphs (for example, the deletion of an ingredient common to many drug products) in accordance with a notice, or regulation published in the Federal Register that provides for a less burdensome notification of the change (for example, by notification at the time a supplement is submitted or in the next annual report). Except for a supplemental application providing for a change in the labeling, the applicant, other than a foreign applicant, shall include in each supplemental application providing for a change under paragraph (b) or (c) of this section a statement certifying that a field copy of the supplement has been provided to the applicant's home FDA district office.

(b) Supplements requiring FDA approval before the change is made. An applicant shall submit a supplement, and obtain FDA approval of it, before making the changes listed below in the conditions in an approved application, unless the change is made to comply with an official compendium. An applicant may ask FDA to expedite its review of a supplement if a delay in making the change described in it would impose an extraordinary hardship on the applicant. Such a supplement and its mailing cover should be plainly marked: “Supplement--Expedited Review Requested.”

(1) Drug substance. A change affecting the drug substance to accomplish any of the following:
   (i) To relax the limits for a specification;
   (ii) To establish a new regulatory analytical method;
   (iii) To delete a specification or regulatory analytical method;
   (iv) To change the synthesis of the drug substance, including a change in solvents and a change in the route of synthesis.
   (v) To use a different facility or establishment to manufacture the drug substance, where:
       (a) the manufacturing process in the new facility or establishment differs materially from that in the former facility or establishment, or
(b) the new facility or establishment has not received a satisfactory current good manufacturing practice (CGMP) inspection within the previous 2 years covering that manufacturing process.

(2) Drug product. A change affecting the drug product to accomplish any of the following:
   (i) To add or delete an ingredient, or otherwise to change the composition of the drug product, other than deletion of an ingredient intended only to affect the color of the drug product;
   (ii) To relax the limits for a specification;
   (iii) To establish a new regulatory analytical method;
   (iv) To delete a specification or regulatory analytical method;
   (v) To change the method of manufacture of the drug product, including changing or relaxing an in-process control;
   (vi) To use a different facility or establishment, including a different contract laboratory or labeler, to manufacture, process, or pack the drug product;
   (vii) To change the container and closure system for the drug product (for example, glass to high density polyethylene (HDPE), or HDPE to polyvinyl chloride) or change a specification or regulatory analytical method for the container and closure system;
   (viii) To change the size of the container, except for solid dosage forms, without a change in the container and closure system.
   (ix) To extend the expiration date of the drug product based on data obtained under a new or revised stability testing protocol that has not been approved in the application.
   (x) To establish a new procedure for reprocessing a batch of the drug product that fails to meet specifications.
   (xi) To add a code imprint by printing with ink on a solid oral dosage form drug product.
   (xii) To add a code imprint by embossing, debossing, or engraving on a modified release solid oral dosage form drug product.

(3) Labeling.
   (i) Any change in labeling, except one described in paragraphs (c)(2) or (d) of this section.
   (ii) If applicable, any change to a Medication Guide required under part 208 of this chapter, except for changes in the information specified in §208.20(b)(8)(iii) and (b)(8)(iv).

(c) Supplements for changes that may be made before FDA approval. An applicant shall submit a supplement at the time the applicant makes any kind of change listed below in the conditions in an approved application, unless the change is made to comply with an official compendium. A supplement under this paragraph is required to give a full explanation of the basis for the change, identify the date on which the change is made, and, if the change concerns labeling, include 12 copies of final printed labeling. The applicant shall promptly revise all promotional labeling and drug advertising to make it consistent with any change in the labeling. The supplement and its mailing cover should be plainly marked: “Special Supplement--Changes Being Effected.”
(1) Adds a new specification or test method or changes in the methods, facilities (except a change to a new facility), or controls to provide increased assurance that the drug will have the characteristics of identity, strength, quality, and purity which it purports or is represented to possess;

(2) Changes labeling to accomplish any of the following:
   (i) To add or strengthen a contraindication, warning, precaution, or adverse reaction;
   (ii) To add or strengthen a statement about drug abuse, dependence, or overdosage; or
   (iii) To add or strengthen an instruction about dosage and administration that is intended to increase the safe use of the product.
   (iv) To delete false, misleading, or unsupported indications for use or claims for effectiveness.

(3) To use a different facility or establishment to manufacture the drug substance, where: (i) The manufacturing process in the new facility or establishment does not differ materially from that in the former facility or establishment, and (ii) the new facility or establishment has received a satisfactory current good manufacturing practice (CGMP) inspection within the previous 2 years covering that manufacturing process.

(d) Changes described in the annual report. An applicant shall not submit a supplement to make any change in the conditions in an approved application, unless otherwise required under paragraph (b) or (c) of this section, but shall describe the change in the next annual report required under §314.81. Some examples of changes that can be described in the annual report are the following:
   (1) Any change made to comply with an official compendium.
   (2) A change in the labeling concerning the description of the drug product or in the information about how the drug product is supplied, that does not involve a change in the dosage strength or dosage form.
   (3) An editorial or similar minor change in labeling.
   (4) The deletion of an ingredient intended only to affect the color of the drug product.
   (5) An extension of the expiration date based upon full shelf-life data obtained from a protocol approved in the application.
   (6) A change within the container and closure system for the drug product (for example, a change from one high density polyethylene (HDPE) to another HDPE), except a change in container size for nonsolid dosage forms, based upon a showing of equivalency to the approved system under a protocol approved in the application or published in an official compendium.
   (7) The addition or deletion of an alternate analytical method.
   (8) A change in the size of a container for a solid dosage form, without a change from one container and closure system to another.
   (9) The addition by embossing, debossing, or engraving of a code imprint to a solid oral dosage form drug product other than a modified release dosage form, or a minor change in an existing code imprint.

(e) Patent information. The applicant shall comply with the patent information requirements under section 505(c)(2) of the act.
(f) Claimed exclusivity. If an applicant claims exclusivity under §314.108 upon approval of a supplemental application for a change to its previously approved drug product, the applicant shall include with its supplemental application the information required under §314.50(j).

(g) Exception. An applicant proposing to make a change of a type described in paragraphs (a), (b)(1), (b)(2), (c)(1), (c)(3), (d)(1), and (d)(4) through (d)(9) of this section affecting a recombinant DNA-derived protein/polypeptide product or a complex or conjugate of a drug with a monoclonal antibody regulated under the Federal Food, Drug, and Cosmetic Act shall comply with the following:

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

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

(A) Changes in the qualitative or quantitative formulation or other specifications as provided in the approved application or in the regulations;
(B) Changes requiring completion of an appropriate human study to demonstrate the equivalence of the identity, strength, quality, purity, or potency of the product as they may relate to the safety or effectiveness of the product;
(C) Changes in the virus or adventitious agent removal or inactivation method(s);
(D) Changes in the source material or cell line;
(E) Establishment of a new master cell bank or seed; and
(F) Changes which may affect product sterility assurance, such as changes in product or component sterilization method(s) or an addition, deletion, or substitution of steps in an aseptic processing operation.

(iii) The applicant must obtain approval of the supplement from FDA prior to distribution of the product made using the change. Except for submissions under paragraph (g)(4) of this section, the following shall be contained in the supplement:

(A) A detailed description of the proposed change;
(B) The product(s) involved;
(C) The manufacturing site(s) or area(s) affected;
(D) A description of the methods used and studies performed to evaluate the effect of the change on the identity, strength, quality, purity, or potency of the product as they may relate to the safety or effectiveness of the product;
(E) The data derived from such studies;
(F) Relevant validation protocols and data; and
(G) A reference list of relevant standard operating procedures (SOP's).

(2) Changes requiring supplement submission at least 30 days prior to distribution of the product made using the change.
(i) A supplement shall be submitted for any change in the product, production process, quality controls, equipment, or facilities that has a moderate potential to have an adverse effect on the identity, strength, quality, purity, or potency of the product as they may relate to the safety or effectiveness of the product. The supplement shall be labeled “Supplement--Changes Being Effected in 30 Days” or, if applicable under paragraph (g)(2)(v) of this section, “Supplement--Changes Being Effected.”

(ii) These changes include, but are not limited to:
   (A) Change in the site of testing from one facility to another;
   (B) An increase or decrease in production scale during finishing steps that involves new or different equipment; and
   (C) Replacement of equipment with that of similar, but not identical, design and operating principle that does not affect the process methodology or process operating parameters.

(iii) Pending approval of the supplement by FDA, and except as provided in paragraph (g)(2)(v) of this section, distribution of the product made using the change may begin not less than 30 days after receipt of the supplement by FDA. The information listed in paragraph (g)(1)(iii)(A) through (g)(1)(iii)(G) of this section shall be contained in the supplement.

(iv) If within 30 days following FDA's receipt of the supplement, FDA informs the applicant that either:
   (A) The change requires approval prior to distribution of the product in accordance with paragraph (g)(1) of this section; or
   (B) Any of the information required under paragraph (g)(2)(iii) of this section is missing; the applicant shall not distribute the product made using the change until FDA determines that compliance with this section is achieved.

(v) In certain circumstances, FDA may determine that, based on experience with a particular type of change, the supplement for such change is usually complete and provides the proper information, and on particular assurances that the proposed change has been appropriately submitted, the product made using the change may be distributed immediately upon receipt of the supplement by FDA. These circumstances may include substantial similarity with a type of change regularly involving a “Supplement--Changes Being Effected” supplement, or a situation in which the applicant presents evidence that the proposed change has been validated in accordance with an approved protocol for such change under paragraph (g)(4) of this section.

(3) Changes to be described in an annual report (minor changes).
   (i) Changes in the product, production process, quality controls, equipment, or facilities that have a minimal potential to have an adverse effect on the identity, strength, quality, purity, or potency of the product as they may relate to the safety or effectiveness of the product shall be documented by the applicant in the next annual report in accordance with §314.81(b)(2)(iv).

(ii) These changes include, but are not limited to:
(A) Any change made to comply with an official compendium that is consistent with FDA requirements;
(B) The deletion of an ingredient intended only to affect the color of the product;
(C) An extension of an expiration date based upon full shelf life data obtained from a protocol approved in the application;
(D) A change within the container and closure system for solid dosage forms, based upon a showing of equivalency to the approved system under a protocol approved in the application or published in an official compendium;
(E) A change in the size of a container for a solid dosage form, without a change from one container and closure system to another;
(F) The addition by embossing, debossing, or engraving of a code imprint to a solid dosage form drug product other than a modified release dosage form, or a minor change in an existing code imprint; and
(G) The addition or deletion of an alternate analytical method.

(4) An applicant may submit one or more protocols describing the specific tests and validation studies and acceptable limits to be achieved to demonstrate the lack of adverse effect for specified types of manufacturing changes on the identity, strength, quality, purity, or potency of the product as they may relate to the safety or effectiveness of the product. Any such protocols, or change to a protocol, shall be submitted as a supplement requiring approval from FDA prior to distribution of the product which, if approved, may justify a reduced reporting category for the particular change because the use of the protocol for that type of change reduces the potential risk of an adverse effect.


§314.71 Procedures for submission of a supplement to an approved application.

(a) Only the applicant may submit a supplement to an application.
(b) All procedures and actions that apply to an application under §314.50 also apply to supplements, except that the information required in the supplement is limited to that needed to support the change. A supplement is required to contain an archival copy and a review copy that include an application form and appropriate technical sections, samples, and labeling; except that a supplement for a change other than a change in labeling is required also to contain a field copy.
(c) All procedures and actions that apply to applications under this part, including actions by applicants and the Food and Drug Administration, also apply to supplements.

§314.72 Change in ownership of an application.
(a) An applicant may transfer ownership of its application. At the time of transfer the new and former owners are required to submit information to the Food and Drug Administration as follows:
1. The former owner shall submit a letter or other document that states that all rights to the application have been transferred to the new owner.
2. The new owner shall submit an application form signed by the new owner and a letter or other document containing the following:
   (i) The new owner's commitment to agreements, promises, and conditions made by the former owner and contained in the application;
   (ii) The date that the change in ownership is effective; and
   (iii) Either a statement that the new owner has a complete copy of the approved application, including supplements and records that are required to be kept under §314.81, or a request for a copy of the application from FDA's files. FDA will provide a copy of the application to the new owner under the fee schedule in §20.42 of FDA's public information regulations.
(b) The new owner shall advise FDA about any change in the conditions in the approved application under §314.70, except the new owner may advise FDA in the next annual report about a change in the drug product's label or labeling to change the product's brand or the name of its manufacturer, packer, or distributor.


§314.80 Postmarketing reporting of adverse drug experiences.
(a) Definitions. The following definitions of terms apply to this section:-

- **Adverse drug experience.** Any adverse event associated with the use of a drug in humans, whether or not considered drug related, including the following: An adverse event occurring in the course of the use of a drug product in professional practice; an adverse event occurring from drug overdose whether accidental or intentional; an adverse event occurring from drug abuse; an adverse event occurring from drug withdrawal; and any failure of expected pharmacological action.

- **Disability.** A substantial disruption of a person's ability to conduct normal life functions. Life-threatening adverse drug experience. Any adverse drug experience that places the patient, in the view of the initial reporter, at immediate risk of death from the adverse drug experience as it occurred, i.e., it does not include an adverse drug experience that, had it occurred in a more severe form, might have caused death.

- **Serious adverse drug experience.** Any adverse drug experience occurring at any dose that results in any of the following outcomes: Death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may
jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

**Unexpected adverse drug experience.** Any adverse drug experience that is not listed in the current labeling for the drug product. This includes events that may be symptomatically and pathophysiological related to an event listed in the labeling, but differ from the event because of greater severity or specificity. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the labeling only referred to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the labeling only listed cerebral vascular accidents. “Unexpected,” as used in this definition, refers to an adverse drug experience that has not been previously observed (i.e., included in the labeling) rather than from the perspective of such experience not being anticipated from the pharmacological properties of the pharmaceutical product.

(b) Review of adverse drug experiences. Each applicant having an approved application under §314.50 or, in the case of a 505(b)(2) application, an effective approved application, shall promptly review all adverse drug experience information obtained or otherwise received by the applicant from any source, foreign or domestic, including information derived from commercial marketing experience, postmarketing clinical investigations, postmarketing epidemiological/surveillance studies, reports in the scientific literature, and unpublished scientific papers. Applicants are not required to resubmit to FDA adverse drug experience reports forwarded to the applicant by FDA; however, applicants must submit all followup information on such reports to FDA. Any person subject to the reporting requirements under paragraph (c) of this section shall also develop written procedures for the surveillance, receipt, evaluation, and reporting of postmarketing adverse drug experiences to FDA.

(c) Reporting requirements. The applicant shall report to FDA adverse drug experience information, as described in this section. The applicant shall submit two copies of each report described in this section to the Central Document Room, 12229 Wilkins Ave., Rockville, MD 20852. FDA may waive the requirement for the second copy in appropriate instances.

(1) (i) Postmarketing 15-day “Alert reports”. The applicant shall report each adverse drug experience that is both serious and unexpected, whether foreign or domestic, as soon as possible but in no case later than 15 calendar days of initial receipt of the information by the applicant.

(ii) Postmarketing 15-day “Alert reports”--followup. The applicant shall promptly investigate all adverse drug experiences that are the subject of these postmarketing 15-day Alert reports and shall submit followup reports within 15 calendar days of receipt of new information or as requested by FDA. If additional information is not obtainable, records should be maintained of the unsuccessful steps taken to seek additional
information. Postmarketing 15-day Alert reports and followups to them shall be submitted under separate cover.

(iii) Submission of reports. The requirements of paragraphs (c)(1)(i) and (c)(1)(ii) of this section, concerning the submission of postmarketing 15-day Alert reports, shall also apply to any person other than the applicant (nonapplicant) whose name appears on the label of an approved drug product as a manufacturer, packer, or distributor. To avoid unnecessary duplication in the submission to FDA of reports required by paragraphs (c)(1)(i) and (c)(1)(ii) of this section, obligations of a nonapplicant may be met by submission of all reports of serious adverse drug experiences to the applicant. If a nonapplicant elects to submit adverse drug experience reports to the applicant rather than to FDA, the nonapplicant shall submit each report to the applicant within 5 calendar days of receipt of the report by the nonapplicant, and the applicant shall then comply with the requirements of this section. Under this circumstance, the nonapplicant shall maintain a record of this action which shall include:

(A) A copy of each adverse drug experience report;
(B) The date the report was received by the nonapplicant;
(C) The date the report was submitted to the applicant; and
(D) The name and address of the applicant.

(iv) Report identification. Each report submitted under this paragraph shall bear prominent identification as to its contents, i.e., “15-day Alert report,” or “15-day Alert report-followup.”

(2) Periodic adverse drug experience reports. (i) The applicant shall report each adverse drug experience not reported under paragraph (c)(1)(i) of this section at quarterly intervals, for 3 years from the date of approval of the application, and then at annual intervals. The applicant shall submit each quarterly report within 30 days of the close of the quarter (the first quarter beginning on the date of approval of the application) and each annual report within 60 days of the anniversary date of approval of the application. Upon written notice, FDA may extend or reestablish the requirement that an applicant submit quarterly reports, or require that the applicant submit reports under this section at different times than those stated. For example, the agency may reestablish a quarterly reporting requirement following the approval of a major supplement. Followup information to adverse drug experiences submitted in a periodic report may be submitted in the next periodic report.

(ii) Each periodic report is required to contain:

(a) a narrative summary and analysis of the information in the report and an analysis of the 15-day Alert reports submitted during the reporting interval (all 15-day Alert reports being appropriately referenced by the applicant's patient identification number, adverse reaction term(s), and date of submission to FDA);

(b) a FDA Form 3500A (Adverse Reaction Report) for each adverse drug experience not reported under paragraph (c)(1)(i) of this section (with an index consisting of a line listing of the applicant's patient identification number and adverse reaction term(s)); and
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(c) a history of actions taken since the last report because of adverse drug experiences (for example, labeling changes or studies initiated).
(iii) Periodic reporting, except for information regarding 15-day Alert reports, does not apply to adverse drug experience information obtained from postmarketing studies (whether or not conducted under an investigational new drug application), from reports in the scientific literature, and from foreign marketing experience.

(d) Scientific literature.
(1) A 15-day Alert report based on information from the scientific literature is required to be accompanied by a copy of the published article. The 15-day reporting requirements in paragraph (c)(1)(i) of this section (i.e., serious, unexpected adverse drug experiences) apply only to reports found in scientific and medical journals either as case reports or as the result of a formal clinical trial.
(2) As with all reports submitted under paragraph (c)(1)(i) of this section, reports based on the scientific literature shall be submitted on FDA Form 3500A or comparable format as prescribed by paragraph (f) of this section. In cases where the applicant believes that preparing the FDA Form 3500A constitutes an undue hardship, the applicant may arrange with the Division of Pharmacovigilance and Epidemiology for an acceptable alternative reporting format.

(e) Postmarketing studies.
(1) An applicant is not required to submit a 15-day Alert report under paragraph (c) of this section for an adverse drug experience obtained from a postmarketing study (whether or not conducted under an investigational new drug application) unless the applicant concludes that there is a reasonable possibility that the drug caused the adverse experience.
(2) The applicant shall separate and clearly mark reports of adverse drug experiences that occur during a postmarketing study as being distinct from those experiences that are being reported spontaneously to the applicant.

(f) Reporting FDA Form 3500A.
(1) Except as provided in paragraph (f)(3) of this section, the applicant shall complete FDA Form 3500A for each report of an adverse drug experience (foreign events may be submitted either on an FDA Form 3500A or, if preferred, on a CIOMS I form).
(2) Each completed FDA Form 3500A should refer only to an individual patient or a single attached publication.
(3) Instead of using FDA Form 3500A, an applicant may use a computer-generated FDA Form 3500A or other alternative format (e.g., a computer-generated tape or tabular listing) provided that: (i) The content of the alternative format is equivalent in all elements of information to those specified in FDA Form 3500A; and (ii) The format is agreed to in advance by MedWatch: The FDA Medical Products Reporting Program.
(4) Ten copies or fewer of FDA Form 3500A and/or a copy of the instructions for completing the form may be obtained from the Division of Pharmacovigilance and Epidemiology (HFD-730), Center for Drug Evaluation and Research, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857. More than
10 copies of the form may be obtained by writing to the Consolidated Forms and Publications Distribution Center, Washington Commerce Center, 3222 Hubbard Rd., Landover, MD 20785.

(g) Multiple reports. An applicant should not include in reports under this section any adverse drug experiences that occurred in clinical trials if they were previously submitted as part of the approved application. If a report applies to a drug for which an applicant holds more than one approved application, the applicant should submit the report to the application that was first approved. If a report refers to more than one drug marketed by an applicant, the applicant should submit the report to the application for the drug listed first in the report.

(h) Patient privacy. An applicant should not include in reports under this section the names and addresses of individual patients; instead, the applicant should assign a unique code number to each report, preferably not more than eight characters in length. The applicant should include the name of the reporter from whom the information was received. Names of patients, health care professionals, hospitals, and geographical identifiers in adverse drug experience reports are not releasable to the public under FDA's public information regulations in part 20.

(i) Recordkeeping. The applicant shall maintain for a period of 10 years records of all adverse drug experiences known to the applicant, including raw data and any correspondence relating to adverse drug experiences.

(j) Withdrawal of approval. If an applicant fails to establish and maintain records and make reports required under this section, FDA may withdraw approval of the application and, thus, prohibit continued marketing of the drug product that is the subject of the application.

(k) Disclaimer. A report or information submitted by an applicant under this section (and any release by FDA of that report or information) does not necessarily reflect a conclusion by the applicant or FDA that the report or information constitutes an admission that the drug caused or contributed to an adverse effect. An applicant need not admit, and may deny, that the report or information submitted under this section constitutes an admission that the drug caused or contributed to an adverse effect. For purposes of this provision, the term “applicant” also includes any person reporting under paragraph (c)(1)(iii) of this section.


§314.81 Other postmarketing reports.

(a) Applicability. Each applicant shall make the reports for each of its approved applications and abbreviated applications required under this section and section 505(k) of the act.

(b) Reporting requirements. The applicant shall submit to the Food and Drug Administration at the specified times two copies of the following reports:

(1) NDA--Field alert report. The applicant shall submit information of the following kinds about distributed drug products and articles to the FDA district office that is responsible for the facility involved within 3 working days of receipt by the
applicant. The information may be provided by telephone or other rapid communication means, with prompt written followup. The report and its mailing cover should be plainly marked: “NDA--Field Alert Report.”

(i) Information concerning any incident that causes the drug product or its labeling to be mistaken for, or applied to, another article.

(ii) Information concerning any bacteriological contamination, or any significant chemical, physical, or other change or deterioration in the distributed drug product, or any failure of one or more distributed batches of the drug product to meet the specifications established for it in the application.

(2) Annual report. The applicant shall submit each year within 60 days of the anniversary date of U.S. approval of the application, two copies of the report to the FDA division responsible for reviewing the application. Each annual report is required to be accompanied by a completed transmittal Form FDA 2252 (Transmittal of Periodic Reports for Drugs for Human Use), and must include all the information required under this section that the applicant received or otherwise obtained during the annual reporting interval that ends on the U.S. anniversary date. The report is required to contain in the order listed:

(i) Summary. A brief summary of significant new information from the previous year that might affect the safety, effectiveness, or labeling of the drug product. The report is also required to contain a brief description of actions the applicant has taken or intends to take as a result of this new information, for example, submit a labeling supplement, add a warning to the labeling, or initiate a new study. The summary shall briefly state whether labeling supplements for pediatric use have been submitted and whether new studies in the pediatric population to support appropriate labeling for the pediatric population have been initiated. Where possible, an estimate of patient exposure to the drug product, with special reference to the pediatric population (neonates, infants, children, and adolescents) shall be provided, including dosage form.

(ii) Distribution data. Information about the quantity of the drug product distributed under the approved application, including that distributed to distributors. The information is required to include the National Drug Code (NDC) number, the total number of dosage units of each strength or potency distributed (e.g., 100,000/5 milligram tablets, 50,000/10 milliliter vials), and the quantities distributed for domestic use and the quantities distributed for foreign use. Disclosure of financial or pricing data is not required.

(iii) Labeling. Currently used professional labeling, patient brochures or package inserts (if any), a representative sample of the package labels, and a summary of any changes in labeling that have been made since the last report listed by date in the order in which they were implemented, or if no changes, a statement of that fact.

(iv) Chemistry, manufacturing, and controls changes.

(a) Reports of experiences, investigations, studies, or tests involving chemical or physical properties, or any other properties of the drug
(such as the drug's behavior or properties in relation to microorganisms, including both the effects of the drug on microorganisms and the effects of microorganisms on the drug). These reports are only required for new information that may affect FDA's previous conclusions about the safety or effectiveness of the drug product.

(b) A full description of the manufacturing and controls changes not requiring a supplemental application under §314.70 (b) and (c), listed by date in the order in which they were implemented.

(v) Nonclinical laboratory studies. Copies of unpublished reports and summaries of published reports of new toxicological findings in animal studies and in vitro studies (e.g., mutagenicity) conducted by, or otherwise obtained by, the applicant concerning the ingredients in the drug product. The applicant shall submit a copy of a published report if requested by FDA.

(vi) Clinical data.

(a) Published clinical trials of the drug (or abstracts of them), including clinical trials on safety and effectiveness; clinical trials on new uses; biopharmaceutic, pharmacokinetic, and clinical pharmacology studies; and reports of clinical experience pertinent to safety (for example, epidemiologic studies or analyses of experience in a monitored series of patients) conducted by or otherwise obtained by the applicant. Review articles, papers describing the use of the drug product in medical practice, papers and abstracts in which the drug is used as a research tool, promotional articles, press clippings, and papers that do not contain tabulations or summaries of original data should not be reported.

(b) Summaries of completed unpublished clinical trials, or prepublication manuscripts if available, conducted by, or otherwise obtained by, the applicant. Supporting information should not be reported. (A study is considered completed 1 year after it is concluded.)

(c) Analysis of available safety and efficacy data in the pediatric population and changes proposed in the labeling based on this information. An assessment of data needed to ensure appropriate labeling for the pediatric population shall be included.

(vii) Status reports of postmarketing study commitments. A status report of each postmarketing study of the drug product concerning clinical safety, clinical efficacy, clinical pharmacology, and nonclinical toxicology that is required by FDA (e.g., accelerated approval clinical benefit studies, pediatric studies) or that the applicant has committed, in writing, to conduct either at the time of approval of an application for the drug product or a supplement to an application, or after approval of the application or a supplement. For pediatric studies, the status report shall include a statement indicating whether postmarketing clinical studies in pediatric populations were required by FDA under §201.23 of this chapter. The status of these postmarketing studies shall be reported annually until
FDA notifies the applicant, in writing, that the agency concurs with the applicant's determination that the study commitment has been fulfilled or that the study is either no longer feasible or would no longer provide useful information.

(a) Content of status report. The following information must be provided for each postmarketing study reported under this paragraph:

1. Applicant's name.
2. Product name. Include the approved drug product's established name and proprietary name, if any.
3. NDA, ANDA, and supplement number.
4. Date of U.S. approval of NDA or ANDA.
5. Date of postmarketing study commitment.
6. Description of postmarketing study commitment. The description must include sufficient information to uniquely describe the study. This information may include the purpose of the study, the type of study, the patient population addressed by the study and the indication(s) and dosage(s) that are to be studied.
7. Schedule for completion and reporting of the postmarketing study commitment. The schedule should include the actual or projected dates for submission of the study protocol to FDA, completion of patient accrual or initiation of an animal study, completion of the study, submission of the final study report to FDA, and any additional milestones or submissions for which projected dates were specified as part of the commitment. In addition, it should include a revised schedule, as appropriate. If the schedule has been previously revised, provide both the original schedule and the most recent, previously submitted revision.
8. Current status of the postmarketing study commitment. The status of each postmarketing study should be categorized using one of the following terms that describes the study's status on the anniversary date of U.S. approval of the application or other agreed upon date:
   (i) Pending. The study has not been initiated, but does not meet the criterion for delayed.
   (ii) Ongoing. The study is proceeding according to or ahead of the original schedule described under paragraph (b)(2)(vii)(a)(7) of this section.
   (iii) Delayed. The study is behind the original schedule described under paragraph (b)(2)(vii)(a)(7) of this section.
   (iv) Terminated. The study was ended before completion but a final study report has not been submitted to FDA.
   (v) Submitted. The study has been completed or terminated and a final study report has been submitted to FDA.
9. Explanation of the study's status. Provide a brief description of the status of the study, including the patient accrual rate (expressed by providing the number of patients or subjects enrolled to date, and the total planned enrollment), and an explanation of the study's
status identified under paragraph (b)(2)(vii)(a)(8) of this section. If the study has been completed, include the date the study was completed and the date the final study report was submitted to FDA, as applicable. Provide a revised schedule, as well as the reason(s) for the revision, if the schedule under paragraph (b)(2)(vii)(a)(7) of this section has changed since the last report.

(b) Public disclosure of information. Except for the information described in this paragraph, FDA may publicly disclose any information described in paragraph (b)(2)(vii) of this section, concerning a postmarketing study, if the agency determines that the information is necessary to identify the applicant or to establish the status of the study, including the reasons, if any, for failure to conduct, complete, and report the study. Under this section, FDA will not publicly disclose trade secrets, as defined in §20.61 of this chapter, or information, described in §20.63 of this chapter, the disclosure of which would constitute an unwarranted invasion of personal privacy.

(viii) Status of other postmarketing studies. A status report of any postmarketing study not included under paragraph (b)(2)(vii) of this section that is being performed by, or on behalf of, the applicant. A status report is to be included for any chemistry, manufacturing, and controls studies that the applicant has agreed to perform and for all product stability studies.

(ix) Log of outstanding regulatory business. To facilitate communications between FDA and the applicant, the report may, at the applicant's discretion, also contain a list of any open regulatory business with FDA concerning the drug product subject to the application (e.g., a list of the applicant's unanswered correspondence with the agency, a list of the agency's unanswered correspondence with the applicant).

(3) Other reporting—

(i) Advertisements and promotional labeling. The applicant shall submit specimens of mailing pieces and any other labeling or advertising devised for promotion of the drug product at the time of initial dissemination of the labeling and at the time of initial publication of the advertisement for a prescription drug product. Mailing pieces and labeling that are designed to contain samples of a drug product are required to be complete, except the sample of the drug product may be omitted. Each submission is required to be accompanied by a completed transmittal Form FDA-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) and is required to include a copy of the product's current professional labeling. Form FDA-2253 may be obtained from the PHS Forms and Publications Distribution Center, 12100 Parklawn Dr., Rockville, MD 20857.

(ii) Special reports. Upon written request the agency may require that the applicant submit the reports under this section at different times than those stated.

(iii) Withdrawal of approved drug product from sale.
(a) The applicant shall submit on Form FDA 2657 (Drug Product Listing), within 15 working days of the withdrawal from sale of a drug product, the following information:

1. The National Drug Code (NDC) number.
2. The identity of the drug product by established name and by proprietary name.
3. The new drug application or abbreviated application number.
4. The date of withdrawal from sale. It is requested but not required that the reason for withdrawal of the drug product from sale be included with the information.

(b) The applicant shall submit each Form FDA-2657 to the Drug Listing Branch (HFD-334), Center for Drug Evaluation and Research, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857.

(c) Reporting under paragraph (b)(3)(iii) of this section constitutes compliance with the requirements under §207.30(a) of this chapter to report “at the discretion of the registrant when the change occurs.”

(c) General requirements—

1. Multiple applications. For all reports required by this section, the applicant shall submit the information common to more than one application only to the application first approved, and shall not report separately on each application. The submission is required to identify all the applications to which the report applies.

2. Patient identification. Applicants should not include in reports under this section the names and addresses of individual patients; instead, the applicant should code the patient names whenever possible and retain the code in the applicant's files. The applicant shall maintain sufficient patient identification information to permit FDA, by using that information alone or along with records maintained by the investigator of a study, to identify the name and address of individual patients; this will ordinarily occur only when the agency needs to investigate the reports further or when there is reason to believe that the reports do not represent actual results obtained.

(d) Withdrawal of approval. If an applicant fails to make reports required under this section, FDA may withdraw approval of the application and, thus, prohibit continued marketing of the drug product that is the subject of the application. (Collection of information requirements approved by the Office of Management and Budget under control number 0910-0001)

§314.81 Other postmarketing reports.

(b) * * *
(2) Annual report. The applicant shall submit each year within 60 days of the anniversary date of U.S. approval of the application, two copies of the report to the FDA division responsible for reviewing the application. Each annual report is required to be accompanied by a completed transmittal Form FDA 2252 (Transmittal of Periodic Reports for Drugs for Human Use), and must include all the information required under this section that the applicant received or otherwise obtained during the annual reporting interval that ends on the U.S. anniversary date. The report is required to contain in the order listed: * * * * *(vii) Status reports of postmarketing study commitments. A status report of each postmarketing study of the drug product concerning clinical safety, clinical efficacy, clinical pharmacology, and nonclinical toxicology that is required by FDA (e.g., accelerated approval clinical benefit studies, pediatric studies) or that the applicant has committed, in writing, to conduct either at the time of approval of an application for the drug product or a supplement to an application, or after approval of the application or a supplement. For pediatric studies, the status report shall include a statement indicating whether postmarketing clinical studies in pediatric populations were required by FDA under §201.23 of this chapter. The status of these postmarketing studies shall be reported annually until FDA notifies the applicant, in writing, that the agency concurs with the applicant's determination that the study commitment has been fulfilled or that the study is either no longer feasible or would no longer provide useful information.

(a) Content of status report. The following information must be provided for each postmarketing study reported under this paragraph:

(1) Applicant's name.
(2) Product name. Include the approved drug product's established name and proprietary name, if any.
(3) NDA, ANDA, and supplement number.
(4) Date of U.S. approval of NDA or ANDA.
(5) Date of postmarketing study commitment.
(6) Description of postmarketing study commitment. The description must include sufficient information to uniquely describe the study. This information may include the purpose of the study, the type of study, the patient population addressed by the study and the indication(s) and dosage(s) that are to be studied.
(7) Schedule for completion and reporting of the postmarketing study commitment. The schedule should include the actual or projected dates for submission of the study protocol to FDA, completion of patient accrual or initiation of an animal study, completion of the study, submission of the final study report to FDA, and any additional milestones or submissions for which projected dates were specified as part of the commitment. In addition, it should include a revised schedule, as appropriate. If the schedule has been previously revised, provide both the original schedule and the most recent, previously submitted revision.
(8) Current status of the postmarketing study commitment. The status of each postmarketing study should be categorized using one of the following terms that describes the study’s status on the anniversary date of U.S. approval of the application or other agreed upon date:

(i) Pending. The study has not been initiated, but does not meet the criterion for delayed.

(ii) Ongoing. The study is proceeding according to or ahead of the original schedule described under paragraph (b)(2)(vii)(a)(7) of this section.

(iii) Delayed. The study is behind the original schedule described under paragraph (b)(2)(vii)(a)(7) of this section.

(iv) Terminated. The study was ended before completion but a final study report has not been submitted to FDA.

(v) Submitted. The study has been completed or terminated and a final study report has been submitted to FDA.

(9) Explanation of the study’s status. Provide a brief description of the status of the study, including the patient accrual rate (expressed by providing the number of patients or subjects enrolled to date, and the total planned enrollment), and an explanation of the study’s status identified under paragraph (b)(2)(vii)(a)(8) of this section. If the study has been completed, include the date the study was completed and the date the final study report was submitted to FDA, as applicable. Provide a revised schedule, as well as the reason(s) for the revision, if the schedule under paragraph (b)(2)(vii)(a)(7) of this section has changed since the last report.

(b) Public disclosure of information. Except for the information described in this paragraph, FDA may publicly disclose any information described in paragraph (b)(2)(vii) of this section, concerning a postmarketing study, if the agency determines that the information is necessary to identify the applicant or to establish the status of the study, including the reasons, if any, for failure to conduct, complete, and report the study. Under this section, FDA will not publicly disclose trade secrets, as defined in §20.61 of this chapter, or information, described in §20.63 of this chapter, the disclosure of which would constitute an unwarranted invasion of personal privacy.

(viii) Status of other postmarketing studies. A status report of any postmarketing study not included under paragraph (b)(2)(vii) of this section that is being performed by, or on behalf of, the applicant. A status report is to be included for any chemistry, manufacturing, and controls studies that the applicant has agreed to perform and for all product stability studies.

(ix) Log of outstanding regulatory business. To facilitate communications between FDA and the applicant, the report may, at the applicant's discretion, also contain a list of any open regulatory business with FDA concerning the drug product subject to the application (e.g., a list of the applicant's unanswered correspondence with the agency, a list of the agency's unanswered correspondence with the applicant).
§314.90 Waivers.
(a) An applicant may ask the Food and Drug Administration to waive under this section any requirement that applies to the applicant under §§314.50 through 314.81. An applicant may ask FDA to waive under §314.126(c) any criteria of an adequate and well-controlled study described in §314.126(b). A waiver request under this section is required to be submitted with supporting documentation in an application, or in an amendment or supplement to an application. The waiver request is required to contain one of the following:
   (1) An explanation why the applicant's compliance with the requirement is unnecessary or cannot be achieved;
   (2) A description of an alternative submission that satisfies the purpose of the requirement; or
   (3) Other information justifying a waiver.
(b) FDA may grant a waiver if it finds one of the following:
   (1) The applicant's compliance with the requirement is unnecessary for the agency to evaluate the application or compliance cannot be achieved;
   (2) The applicant's alternative submission satisfies the requirement; or
   (3) The applicant's submission otherwise justifies a waiver.


Subpart C--Abbreviated Applications

§314.92 Drug products for which abbreviated applications may be submitted.

Source: 57 FR 17983, Apr. 28, 1992, unless otherwise noted.

(a) Abbreviated applications are suitable for the following drug products within the limits set forth under §314.93:
   (1) Drug products that are the same as a listed drug. A “listed drug” is defined in §314.3. For determining the suitability of an abbreviated new drug application, the term “same as” means identical in active ingredient(s), dosage form, strength, route of administration, and conditions of use, except that conditions of use for which approval cannot be granted because of exclusivity or an existing patent may be omitted. If a listed drug has been voluntarily withdrawn from or not offered for sale by its manufacturer, a person who wishes to submit an abbreviated new drug application for the drug shall comply with §314.122.
   (2) [Reserved]
   (3) Drug products that have been declared suitable for an abbreviated new drug application submission by FDA through the petition procedures set forth under §10.30 of this chapter and §314.93.
(b) FDA will publish in the list listed drugs for which abbreviated applications may be submitted. The list is available from the Superintendent of Documents, U.S. Government Printing Office, Washington, DC 20402, 202-783-3238.

[57 FR 17983, Apr. 28, 1992, as amended at 64 FR 401, Jan. 5, 1999]
§314.93 Petition to request a change from a listed drug.

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

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

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

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

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

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

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

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

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

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

   (ii) For a petition that seeks to change an active ingredient, the drug product that is the subject of the petition is not a combination drug; or
(iii) For a combination drug product that is the subject of the petition and has an active ingredient different from the reference listed drug:

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

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

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

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

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

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

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

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

(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. The archival copy of the abbreviated new drug application is required to contain a 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 of 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 containing that ingredient and approved for the same indication as the proposed drug product or is bioequivalent to a drug product offered for that indication which does not meet the definition of “new drug” under section 201(p) of the act.

(iii) For each in vivo 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 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 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 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 shall contain the same inactive ingredients 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 provided that the applicant identifies and characterizes the differences and provides information demonstrating that the differences do not affect the safety 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 receipt 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.

§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 agent in the United States authorized to accept
service of process for the applicant.

(d) Amendment to an abbreviated application. If an abbreviated application is amended to
include the certification described in §314.94(a)(12)(i)(A)(4), the applicant shall send
the notice required by paragraph (a) of this section at the same time that the
amendment to the abbreviated application is submitted to FDA.

(e) Documentation of receipt of notice. The applicant shall amend its abbreviated
application to document receipt of the notice required under paragraph (a) of this
section by each person provided the notice. The applicant shall include a copy of the
return receipt or other similar evidence of the date the notification was received. FDA
will accept as adequate documentation of the date of receipt a return receipt or a letter
acknowledging receipt by the person provided the notice. An applicant may rely on
another form of documentation only if FDA has agreed to such documentation in
advance. A copy of the notice itself need not be submitted to the agency.

(f) Approval. If the requirements of this section are met, FDA will presume the notice to
be complete and sufficient, and it will count the day following the date of receipt of
the notice by the patent owner or its representative and by the approved application
holder as the first day of the 45-day period provided for in section 505(j)(4)(B)(iii) of
the act. FDA may, if the applicant provides a written statement to FDA that a later
date should be used, count from such later date.

[59 FR 50366, Oct. 3, 1994]

§314.96 Amendments to an unapproved abbreviated application.

(a) Abbreviated new drug application.

(1) An applicant may amend an abbreviated new drug application that is submitted
under §314.94, but not yet approved, to revise existing information or provide
additional information.

(2) Submission of an amendment containing significant data or information
constitutes an agreement between FDA and the applicant to extend the review
period only for the time necessary to review the significant data or information
and for no more than 180 days.

(3) Submission of an amendment containing significant data or information to resolve
deficiencies in the application as set forth in a not approvable letter issued under
§314.120 constitutes an agreement between FDA and the applicant under
section 505(j)(4)(A) of the act to extend the date by which the agency is
required to reach a decision on the abbreviated new drug application only for
the time necessary to review the significant data or information and for no more
than 180 days.

(b) The applicant shall submit a field copy of each amendment to §314.94(a)(9). The
applicant, other than a foreign applicant, shall include in its submission of each such
amendment to FDA a statement certifying that a field copy of the amendment has
been sent to the applicant's home FDA district office.
§314.97 Supplements and other changes to an approved abbreviated application.
The applicant shall comply with the requirements of §§314.70 and 314.71 regarding the submission of supplemental applications and other changes to an approved abbreviated application.

§314.98 Postmarketing reports.
(a) Except as provided in paragraph (b) of this section, each applicant having an approved abbreviated new drug application under §314.94 that is effective shall comply with the requirements of §314.80 regarding the reporting and recordkeeping of adverse drug experiences.
(b) Each applicant shall submit one copy of each report required under §314.80 to the Division of Epidemiology and Surveillance (HFD-730), Center for Drug Evaluation and Research, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857.
(c) Each applicant shall make the reports required under §314.81 and section 505(k) of the act for each of its approved abbreviated applications.

§314.99 Other responsibilities of an applicant of an abbreviated application.
(a) An applicant shall comply with the requirements of §314.65 regarding withdrawal by the applicant of an unapproved abbreviated application and §314.72 regarding a change in ownership of an abbreviated application.
(b) An applicant may ask FDA to waive under this section any requirement that applies to the applicant under §§314.92 through 314.99. The applicant shall comply with the requirements for a waiver under §314.90.

Subpart D--FDA Action on Applications and Abbreviated Applications

§314.100 Timeframes for reviewing applications and abbreviated applications.
(a) Within 180 days of receipt of an application for a new drug under section 505(b) of the act, or of an abbreviated application for a new drug under section 505(j) of the act, FDA will review it and send the applicant either an approval letter under §314.105, or an approvable letter under §314.110, or a not approvable letter under §314.120. This 180-day period is called the “review clock.”
FDA Human Research Regulations

(b) During the review period, an applicant may withdraw an application under §314.65 or an abbreviated application under §314.99 and later resubmit it. FDA will treat the resubmission as a new application or abbreviated application.

(c) The review clock may be extended by mutual agreement between FDA and an applicant or as provided in §§314.60 and 314.96, as the result of a major amendment.

[57 FR 17987, Apr. 28, 1992, as amended at 64 FR 402, Jan. 5, 1999]

§314.101 Filing an application and receiving an abbreviated new drug application.

(a)

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

(2) If FDA finds that none of the reasons in paragraphs (d) and (e) of this section for refusing to file the application apply, the agency will file the application and notify the applicant in writing. The date of filing will be the date 60 days after the date FDA received the application. The date of filing begins the 180-day period described in section 505(c) of the act. This 180-day period is called the “filing clock.”

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

(b)

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

(2) If FDA finds that none of the reasons in paragraphs (d) and (e) of this section for considering the abbreviated new drug application not to have been received applies, the agency will receive the abbreviated new drug application and notify the applicant in writing.
(3) If FDA considers the abbreviated new drug application not to have been received under paragraph (d) or (e) of this section, FDA will notify the applicant, ordinarily by telephone. The applicant may then:
   (i) Withdraw the abbreviated new drug application under §314.99; or
   (ii) Amend the abbreviated new drug application to correct the deficiencies; or
   (iii) Take no action, in which case FDA will refuse to receive the abbreviated new drug application.

(c) [Reserved]

(d) FDA may refuse to file an application or may not consider an abbreviated new drug application to be received if any of the following applies:
   (1) The application does not contain a completed application form.
   (2) The application is not submitted in the form required under §314.50 or §314.94.
   (3) The application or abbreviated application is incomplete because it does not on its face contain information required under section 505(b), section 505(j), or section 507 of the act and §314.50 or §314.94.
   (4) The applicant fails to submit a complete environmental assessment, which addresses each of the items specified in the applicable format under §25.40 of this chapter or fails to provide sufficient information to establish that the requested action is subject to categorical exclusion under §25.30 or §25.31 of this chapter.
   (5) The application or abbreviated application does not contain an accurate and complete English translation of each part of the application that is not in English.
   (6) The application does not contain a statement for each nonclinical laboratory study that it was conducted in compliance with the requirements set forth in part 58 of this chapter, or, for each study not conducted in compliance with part 58 of this chapter, a brief statement of the reason for the noncompliance.
   (7) The application does not contain a statement for each clinical study that it was conducted in compliance with the institutional review board regulations in part 56 of this chapter, or was not subject to those regulations, and that it was conducted in compliance with the informed consent regulations in part 50 of this chapter, or, if the study was subject to but was not conducted in compliance with those regulations, the application does not contain a brief statement of the reason for the noncompliance.
   (8) The drug product that is the subject of the submission is already covered by an approved application or abbreviated application and the applicant of the submission:
      (i) Has an approved application or abbreviated application for the same drug product; or
      (ii) Is merely a distributor and/or repackager of the already approved drug product.
   (9) The application is submitted as a 505(b)(2) application for a drug that is a duplicate of a listed drug and is eligible for approval under section 505(j) of the act.

(e) The agency will refuse to file an application or will consider an abbreviated new drug application not to have been received if any of the following applies:
(1) The drug product is subject to licensing by FDA under the Public Health Service Act (42 U.S.C. 201 et seq.) and subchapter F of this chapter.

(2) In the case of a 505(b)(2) application or an abbreviated new drug application, the drug product contains the same active moiety as a drug that:
   (i) Was approved after September 24, 1984, in an application under section 505(b) of the act, and
   (ii) Is entitled to a 5-year period of exclusivity under section 505(c)(3)(D)(ii) and (j)(4)(D)(ii) of the act and §314.108(b)(2), unless the 5-year exclusivity period has elapsed or unless 4 years of the 5-year period have elapsed and the application or abbreviated application contains a certification of patent invalidity or noninfringement described in §314.50(i)(1)(i)(A)(4) or §314.94(a)(12)(i)(A)(4).

(f) Within 180 days after the date of filing, plus the period of time the review period was extended (if any), FDA will either:
   (i) Approve the application; or
   (ii) Issue a notice of opportunity for hearing if the applicant asked FDA to provide it an opportunity for a hearing on an application in response to an approvable letter or a not approvable letter.

(2) Within 180 days after the date of receipt, plus the period of time the review clock was extended (if any), FDA will either approve or disapprove the abbreviated new drug application. If FDA disapproves the abbreviated new drug application, FDA will issue a notice of opportunity for hearing if the applicant asked FDA to provide it an opportunity for a hearing on an abbreviated new drug application in response to a not approvable letter.

(3) This paragraph does not apply to applications or abbreviated applications that have been withdrawn from FDA review by the applicant.


§314.102 Communications between FDA and applicants.

(a) General principles. During the course of reviewing an application or an abbreviated application, FDA shall communicate with applicants about scientific, medical, and procedural issues that arise during the review process. Such communication may take the form of telephone conversations, letters, or meetings, whichever is most appropriate to discuss the particular issue at hand. Communications shall be appropriately documented in the application in accordance with §10.65 of this chapter. Further details on the procedures for communication between FDA and applicants are contained in a staff manual guide that is publicly available.

(b) Notification of easily correctable deficiencies. FDA reviewers shall make every reasonable effort to communicate promptly to applicants easily correctable deficiencies found in an application or an abbreviated application when those deficiencies are discovered, particularly deficiencies concerning chemistry, manufacturing, and controls issues. The agency will also inform applicants promptly of its need for more data or information or for technical changes in the application or the abbreviated application needed to facilitate the agency's review. This early
communication is intended to permit applicants to correct such readily identified deficiencies relatively early in the review process and to submit an amendment before the review period has elapsed. Such early communication would not ordinarily apply to major scientific issues, which require consideration of the entire pending application or abbreviated application by agency managers as well as reviewing staff. Instead, major scientific issues will ordinarily be addressed in an action letter. (c) Ninety-day conference. Approximately 90 days after the agency receives the application, FDA will provide applicants with an opportunity to meet with agency reviewing officials. The purpose of the meeting will be to inform applicants of the general progress and status of their applications, and to advise applicants of deficiencies that have been identified by that time and that have not already been communicated. This meeting will be available on applications for all new chemical entities and major new indications of marketed drugs. Such meetings will be held at the applicant’s option, and may be held by telephone if mutually agreed upon. Such meetings would not ordinarily be held on abbreviated applications because they are not submitted for new chemical entities or new indications.

(d) End of review conference. At the conclusion of FDA’s review of an application or an abbreviated application as designated by the issuance of an approvable or not approvable letter, FDA will provide applicants with an opportunity to meet with agency reviewing officials. The purpose of the meeting will be to discuss what further steps need to be taken by the applicant before the application or abbreviated application can be approved. This meeting will be available on all applications or abbreviated applications, with priority given to applications for new chemical entities and major new indications for marketed drugs and for the first duplicates for such drugs. Requests for such meetings shall be directed to the director of the division responsible for reviewing the application or abbreviated application.

(e) Other meetings. Other meetings between FDA and applicants may be held, with advance notice, to discuss scientific, medical, and other issues that arise during the review process. Requests for meetings shall be directed to the director of the division responsible for reviewing the application or abbreviated application. FDA will make every attempt to grant requests for meetings that involve important issues and that can be scheduled at mutually convenient times. However, “drop-in” visits (i.e., an unannounced and unscheduled visit by a company representative) are discouraged except for urgent matters, such as to discuss an important new safety issue.

[57 FR 17988, Apr. 28, 1992; 57 FR 29353, July 1, 1992]

§314.103 Dispute resolution.

(a) General. FDA is committed to resolving differences between applicants and FDA reviewing divisions with respect to technical requirements for applications or abbreviated applications as quickly and amicably as possible through the cooperative exchange of information and views.

(b) Administrative and procedural issues. When administrative or procedural disputes arise, the applicant should first attempt to resolve the matter with the division responsible for reviewing the application or abbreviated application, beginning with the consumer safety officer assigned to the application or abbreviated application. If resolution is not achieved, the applicant may raise the matter with the person...
designated as ombudsman, whose function shall be to investigate what has happened and to facilitate a timely and equitable resolution. Appropriate issues to raise with the ombudsman include resolving difficulties in scheduling meetings, obtaining timely replies to inquiries, and obtaining timely completion of pending reviews. Further details on this procedure are contained in a staff manual guide that is publicly available under FDA's public information regulations in part 20.

(c) Scientific and medical disputes.

(1) Because major scientific issues are ordinarily communicated to applicants in an approvable or not approvable letter pursuant to §314.110 or §314.120, respectively, the “end-of-review conference” described in §314.102(d) will provide a timely forum for discussing and resolving, if possible, scientific and medical issues on which the applicant disagrees with the agency. In addition, the “ninety-day conference” described in §314.102(c) will provide a timely forum for discussing and resolving, if possible, issues identified by that date.

(2) When scientific or medical disputes arise at other times during the review process, applicants should discuss the matter directly with the responsible reviewing officials. If necessary, applicants may request a meeting with the appropriate reviewing officials and management representatives in order to seek a resolution. Ordinarily, such meetings would be held first with the Division Director, then with the Office Director, and finally with the Center Director if the matter is still unresolved. Requests for such meetings shall be directed to the director of the division responsible for reviewing the application or abbreviated application. FDA will make every attempt to grant requests for meetings that involve important issues and that can be scheduled at mutually convenient times.

(3) In requesting a meeting designed to resolve a scientific or medical dispute, applicants may suggest that FDA seek the advice of outside experts, in which case FDA may, in its discretion, invite to the meeting one or more of its advisory committee members or other consultants, as designated by the agency. Applicants may also bring their own consultants. For major scientific and medical policy issues not resolved by informal meetings, FDA may refer the matter to one of its standing advisory committees for its consideration and recommendations.


§314.104 Drugs with potential for abuse.

The Food and Drug Administration will inform the Drug Enforcement Administration under section 201(f) of the Controlled Substances Act (21 U.S.C. 801) when an application or abbreviated application is submitted for a drug that appears to have an abuse potential.

[57 FR 17989, Apr. 28, 1992]

§314.105 Approval of an application and an abbreviated application.

(a) The Food and Drug Administration will approve an application and send the applicant an approval letter if none of the reasons in §314.125 for refusing to approve the
application applies. An approval becomes effective on the date of the issuance of the approval letter, except with regard to an approval under section 505(b)(2) of the act with a delayed effective date. An approval with a delayed effective date is tentative and does not become final until the effective date. A new drug product or antibiotic approved under this paragraph may not be marketed until an approval is effective.

(b) FDA will approve an application and issue the applicant an approval letter (rather than an approvable letter under §314.110) on the basis of draft labeling if the only deficiencies in the application concern editorial or similar minor deficiencies in the draft labeling. Such approval will be conditioned upon the applicant incorporating the specified labeling changes exactly as directed, and upon the applicant submitting to FDA a copy of the final printed labeling prior to marketing.

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

(d) FDA will approve an abbreviated new drug application and send the applicant an approval letter if none of the reasons in §314.127 for refusing to approve the abbreviated new drug application applies. The approval becomes effective on the date of the issuance of the agency's approval letter unless the approval letter provides for a delayed effective date. An approval with a delayed effective date is tentative and does not become final until the effective date. A new drug product approved under this paragraph may not be introduced or delivered for introduction into interstate commerce until approval of the abbreviated new drug application is effective. Ordinarily, the effective date of approval will be stated in the approval letter.


§314.106 Foreign data.

(a) General. The acceptance of foreign data in an application generally is governed by §312.120 of this chapter.

(b) As sole basis for marketing approval. An application based solely on foreign clinical data meeting U.S. criteria for marketing approval may be approved if:

(1) The foreign data are applicable to the U.S. population and U.S. medical practice;
(2) the studies have been performed by clinical investigators of recognized competence; and

(3) the data may be considered valid without the need for an on-site inspection by FDA or, if FDA considers such an inspection to be necessary, FDA is able to validate the data through an on-site inspection or other appropriate means. Failure of an application to meet any of these criteria will result in the application not being approvable based on the foreign data alone. FDA will
apply this policy in a flexible manner according to the nature of the drug and the data being considered.

c) Consultation between FDA and applicants. Applicants are encouraged to meet with agency officials in a “presubmission” meeting when approval based solely on foreign data will be sought.


§314.107 Effective date of approval of a 505(b)(2) application or abbreviated new drug application under section 505(j) of the act.

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

(b) Effect of patent on the listed drug. If approval of an abbreviated new drug application submitted under section 505(j) of the act or of a 505(b)(2) application is granted, that approval will become effective in accordance with the following:

(1) Date of approval letter. Except as provided in paragraphs (b)(3), (b)(4), and (c) of this section, approval will become effective on the date FDA issues an approval letter under §314.105 if the applicant certifies under §314.50(i) or §314.94(a)(12) that:

(i) There are no relevant patents; or
(ii) The applicant is aware of a relevant patent but the patent information required under section 505 (b) or (c) of the act has not been submitted to FDA; or
(iii) The relevant patent has expired; or
(iv) The relevant patent is invalid, unenforceable, or will not be infringed.

(2) Patent expiration. If the applicant certifies under §314.50(i) or §314.94(a)(12) that the relevant patent will expire on a specified date, approval will become effective on the specified date.

(3) Disposition of patent litigation.

(i) (A) Except as provided in paragraphs (b)(3)(ii), (b)(3)(iii), and (b)(3)(iv) of this section, if the applicant certifies under §314.50(i) or §314.94(a)(12) that the relevant patent is invalid, unenforceable, or will not be infringed, and the patent owner or its representative or the exclusive patent licensee brings suit for patent infringement within 45 days of receipt by the patent owner of the notice of certification from the applicant under §314.52 or §314.95, approval may be made effective 30 months after the date of the receipt of the notice of certification by the patent owner or by the exclusive licensee (or their representatives) unless the court has extended or reduced the period because of a failure of either the plaintiff or defendant to cooperate reasonably in expediting the action; or
(B) If the patented drug product qualifies for 5 years of exclusive marketing under §314.108(b)(2) and the patent owner or its representative or the exclusive patent licensee brings suit for patent infringement during the 1-year period beginning 4 years after the date the patented drug was approved and within 45 days of receipt by the patent owner of the notice of certification, the approval may be made effective at the expiration of the 7\1/2\ years from the date of approval of the application for the patented drug product.

(ii) If before the expiration of the 30-month period, or 7\1/2\ years where applicable, the court issues a final order that the patent is invalid, unenforceable, or not infringed, approval may be made effective on the date the court enters judgment;

(iii) If before the expiration of the 30-month period, or 7\1/2\ years where applicable, the court issues a final order or judgment that the patent has been infringed, approval may be made effective on the date the court determines that the patent will expire or otherwise orders; or

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

(v) In order for an approval to be made effective under paragraph (b)(3) of this section, the applicant must receive an approval letter from the agency indicating that the application has received final approval. Tentative approval of an application does not constitute “approval” of an application and cannot, absent a final approval letter from the agency, result in an effective approval under paragraph (b)(3) of this section.

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

(c) Subsequent abbreviated new drug application submission.

(1) If an abbreviated new drug application contains a certification that a relevant patent is invalid, unenforceable, or will not be infringed and the application is for a generic copy of the same listed drug for which one or more substantially complete abbreviated new drug applications were previously submitted containing a certification that the same patent was invalid, unenforceable, or would not be infringed, approval of the subsequent abbreviated new drug application will be made effective no sooner than 180 days from whichever of the following dates is earlier:

(i) The date the applicant submitting the first application first commences commercial marketing of its drug product; or
(ii) The date of a decision of the court holding the relevant patent invalid, unenforceable, or not infringed.

(2) For purposes of paragraph (c)(1) of this section, the “applicant submitting the first application” is the applicant that submits an application that is both substantially complete and contains a certification that the patent was invalid, unenforceable, or not infringed prior to the submission of any other application for the same listed drug that is both substantially complete and contains the same certification. A “substantially complete” application must contain the results of any required bioequivalence studies, or, if applicable, a request for a waiver of such studies.

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

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

(d) Delay due to exclusivity. The agency will also delay the effective date of the approval of an abbreviated new drug application under section 505(j) of the act or a 505(b)(2) application if delay is required by the exclusivity provisions in §314.108. When the effective date of an application is delayed under both this section and §314.108, the effective date will be the later of the 2 days specified under this section and §314.108.

(e) Notification of court actions. The applicant shall submit a copy of the entry of the order or judgment to the Office of Generic Drugs (HFD-600), or to the appropriate division in the Office of Drug Evaluation I (HFD-100) or Office of Drug Evaluation II (HFD-500), whichever is applicable, within 10 working days of a final judgment.

(f) Computation of 45-day time clock.

(1) The 45-day clock described in paragraph (b)(3) of this section begins on the day after the date of receipt of the applicant's notice of certification by the patent owner or its representative, and by the approved application holder. When the 45th day falls on Saturday, Sunday, or a Federal holiday, the 45th day will be the next day that is not a Saturday, Sunday, or a Federal holiday.

(2) The abbreviated new drug applicant or the 505(b)(2) applicant shall notify FDA immediately of the filing of any legal action filed within 45 days of receipt of the notice of certification. If the applicant submitting the abbreviated new drug application or the 505(b)(2) application or patent owner or its representative does not notify FDA in writing before the expiration of the 45-day time period or the completion of the agency's review of the application, whichever occurs.
later, that a legal action for patent infringement was filed within 45 days of receipt of the notice of certification, approval of the abbreviated new drug application or the 505(b)(2) application will be made effective immediately upon expiration of the 45 days or upon completion of the agency's review and approval of the application, whichever is later. The notification to FDA of the legal action shall include:

(i) The abbreviated new drug application or 505(b)(2) application number.
(ii) The name of the abbreviated new drug or 505(b)(2) application applicant.
(iii) The established name of the drug product or, if no established name exists, the name(s) of the active ingredient(s), the drug product's strength, and dosage form.
(iv) A certification that an action for patent infringement identified by number, has been filed in an appropriate court on a specified date. The applicant of an abbreviated new drug application shall send the notification to FDA's Office of Generic Drugs (HFD-600). A 505(b)(2) applicant shall send the notification to the appropriate division in the Center for Drug Evaluation and Research reviewing the application. A patent owner or its representative may also notify FDA of the filing of any legal action for patent infringement. The notice should contain the information and be sent to the offices or divisions described in this paragraph.

(3) If the patent owner or approved application holder who is an exclusive patent licensee waives its opportunity to file a legal action for patent infringement within 45 days of a receipt of the notice of certification and the patent owner or approved application holder who is an exclusive patent licensee submits to FDA a valid waiver before the 45 days elapse, approval of the abbreviated new drug application or the 505(b)(2) application will be made effective upon completion of the agency's review and approval of the application. FDA will only accept a waiver in the following form: (Name of patent owner or exclusive patent licensee) has received notice from (name of applicant) under (section 505(b)(3) or 505(j)(2)(B) of the act) and does not intend to file an action for patent infringement against (name of applicant) concerning the drug (name of drug) before (date on which 45 days elapses. (Name of patent owner or exclusive patent licensee) waives the opportunity provided by (section 505(c)(3)(C) or 505(j)(B)(iii) of the act) and does not object to FDA's approval of (name of applicant)'s (505(b)(2) or abbreviated new drug application) for (name of drug) with an immediate effective date on or after the date of this letter.


§314.108 New drug product exclusivity.

(a) Definitions. The following definitions of terms apply to this section:

Active moiety means the molecule or ion, excluding those appended portions of the molecule that cause the drug to be an ester, salt (including a salt with hydrogen or coordination bonds), or other noncovalent derivative (such as a complex, chelate, or clathrate) of the molecule, responsible for the physiological or pharmacological action of the drug substance.
Approved under section 505(b) means an application submitted under section 505(b) and approved on or after October 10, 1962, or an application that was “deemed approved” under section 107(c)(2) of Pub. L. 87-781.

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

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

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

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

FDA means the Food and Drug Administration.

New chemical entity means a drug that contains no active moiety that has been approved by FDA in any other application submitted under section 505(b) of the act.

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

(b) Submission of and effective date of approval of an abbreviated new drug application submitted under section 505(j) of the act or a 505(b)(2) application.

(1) [Reserved]

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

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

(4) If an application:
   (i) Was submitted under section 505(b) of the act;
   (ii) Was approved after September 24, 1984;
   (iii) Was for a drug product that contains an active moiety that has been previously approved in another application under section 505(b) of the act; and
   (iv) Contained reports of new clinical investigations (other than bioavailability studies) conducted or sponsored by the applicant that were essential to approval of the application, the agency will not make effective for a period of 3 years after the date of approval of the application the approval of a 505(b)(2) application or an abbreviated new drug application for the conditions of approval of the original application, or an abbreviated new drug application submitted pursuant to an approved petition under section 505(j)(2)(C) of the act that relies on the information supporting the conditions of approval of an original new drug application.

(5) If a supplemental application:
   (i) Was approved after September 24, 1984; and
   (ii) Contained reports of new clinical investigations (other than bioavailability studies) that were conducted or sponsored by the applicant that were essential to approval of the supplemental application, the agency will not make effective for a period of 3 years after the date of approval of the supplemental application the approval of a 505(b)(2) application or an abbreviated new drug application for a change, or an abbreviated new drug application submitted pursuant to an approved petition under section 505(j)(2)(C) of the act that relies on the information supporting a change approved in the supplemental new drug application.

[59 FR 50368, Oct. 3, 1994]

§314.110 Approvable letter to the applicant.

(a) In selected circumstances, it is useful at the end of the review period for the Food and Drug Administration to indicate to the applicant that the application or abbreviated
application is basically approvable providing certain issues are resolved. An approvable letter may be issued in such circumstances. FDA will send the applicant an approvable letter if the application or abbreviated application substantially meets the requirements of this part and the agency believes that it can approve the application or abbreviated application if specific additional information or material is submitted or specific conditions (for example, certain changes in labeling) are agreed to by the applicant. The approvable letter will describe the information or material FDA requires or the conditions the applicant is asked to meet. As a practical matter, the approvable letter will serve in most instances as a mechanism for resolving outstanding issues on drugs that are about to be approved and marketed. For an application, the applicant shall, within 10 days after the date of the approvable letter:

1. Amend the application or notify FDA of an intent to file an amendment. The filing of an amendment or notice of intent to file an amendment constitutes an agreement by the applicant to extend the review period for 45 days after the date FDA receives the amendment. The extension is to permit the agency to review the amendment;

2. Withdraw the application. FDA will consider the applicant's failure to respond within 10 days to an approvable letter to be a request by the applicant to withdraw the application under §314.65. A decision to withdraw an application is without prejudice to a refiling;

3. For a new drug application, ask the agency to provide the applicant an opportunity for a hearing on the question of whether there are grounds for denying approval of the application under section 505(d) of the act. The applicant shall submit the request to the Associate Director for Policy (HFD-5), Center for Drug Evaluation and Research, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857. Within 60 days of the date of the approvable letter, or within a different time period to which FDA and the applicant agree, the agency will either approve the application under §314.105 or refuse to approve the application under §314.125 and give the applicant written notice of an opportunity for a hearing under §314.200 and section 505(c)(2) of the act on the question of whether there are grounds for denying approval of the application under section 505(d) of the act;

4. [Reserved]

5. Notify FDA that the applicant agrees to an extension of the review period under section 505(c) of the act, so that the applicant can determine whether to respond further under paragraph (a)(1), (a)(2), or (a)(3) of this section. The applicant's notice is required to state the length of the extension. FDA will honor any reasonable request for such an extension. FDA will consider the applicant's failure to respond further within the extended review period to be a request to withdraw the application under §314.65. A decision to withdraw an application is without prejudice to a refiling.

(b) FDA will send the applicant of an abbreviated new drug application an approvable letter only if the application substantially meets the requirements of this part and the agency believes that it can approve the abbreviated application if minor deficiencies (e.g., labeling deficiencies) are corrected. The approvable letter will describe the deficiencies and state a time period within which the applicant must respond. Unless
the applicant corrects the deficiencies by amendment within the specified time period, FDA will refuse to approve the abbreviated application under §314.127. Within 10 days after the date of the approvable letter, the applicant may also ask the agency to provide the applicant an opportunity for a hearing on the question of whether there are grounds for denying approval of the abbreviated new drug application. Applicants who request a hearing shall submit the request to the Associate Director for Policy (HFD-5), Center for Drug Evaluation and Research, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857.


§314.120 Not approvable letter to the applicant.

(a) The Food and Drug Administration will send the applicant a not approvable letter if the agency believes that the application may not be approved for one of the reasons given in §314.125 or the abbreviated new drug application may not be approved for one of the reasons given in §314.127. The not approvable letter will describe the deficiencies in the application or abbreviated application. Except as provided in paragraph (b) of this section, within 10 days after the date of the not approvable letter, the applicant shall:

(1) Amend the application or abbreviated application or notify FDA of an intent to file an amendment. The filing of an amendment or a notice of intent to file an amendment constitutes an agreement by the applicant to extend the review period under §314.60 or §314.96;

(2) Withdraw the application or abbreviated application. Except as provided in paragraph (b) of this section, FDA will consider the applicant's failure to respond within 10 days to a not approvable letter to be a request by the applicant to withdraw the application under §314.65 or abbreviated application under §314.99. A decision to withdraw the application or abbreviated application is without prejudice to refiling;

(3) For a new drug application or an abbreviated application, ask the agency to provide the applicant an opportunity for a hearing on the question of whether there are grounds for denying approval of the application under section 505(d) or (j)(3) of the act. The applicant shall submit the request to the Associate Director for Policy (HFD-5), Center for Drug Evaluation and Research, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857. Within 60 days of the date of the not approvable letter, or within a different time period to which FDA and the applicant agree, the agency will either approve the application or abbreviated application under §314.105 or refuse to approve the application under §314.125 or abbreviated new drug application under §314.127 and give the applicant written notice of an opportunity for a hearing under §314.200 and section 505(c)(1)(B) or (j)(4)(C) of the act on the question of whether there are grounds for denying approval of the application under section 505(d) or (j)(3) of the act; or

(4) [Reserved]

(5) Notify FDA that the applicant agrees to an extension of the review period under section 505(c)(1) or (j)(4)(A) of the act, so that the applicant can determine whether to respond further under paragraph (a)(1), (a)(2), or (a)(3) of this section. The
applicant's notice is required to state the length of the extension. FDA will honor any reasonable request for such an extension. FDA will consider the applicant's failure to respond further within the extended review period to be a request to withdraw the application under §314.65 or abbreviated application under §314.99. A decision to withdraw an application or abbreviated application is without prejudice to a refiling.

(b) With the exception of a request for an opportunity for a hearing under paragraph (a)(3) of this section, the 10-day time period in this section for responding to a not approvable letter does not apply to abbreviated new drug applications. FDA may consider the applicant's failure to respond within 180 days to a not approvable letter to be a request by the applicant to withdraw the abbreviated new drug application under §314.99.


§314.122 Submitting an abbreviated application for, or a 505(j)(2)(C) petition that relies on, a listed drug that is no longer marketed.

(a) An abbreviated new drug application that refers to, or a petition under section 505(j)(2)(C) of the act and §314.93 that relies on, a listed drug that has been voluntarily withdrawn from sale in the United States must be accompanied by a petition seeking a determination whether the listed drug was withdrawn for safety or effectiveness reasons. The petition must be submitted under §§10.25(a) and 10.30 of this chapter and must contain all evidence available to the petitioner concerning the reasons for the withdrawal from sale.

(b) When a petition described in paragraph (a) of this section is submitted, the agency will consider the evidence in the petition and any other evidence before the agency, and determine whether the listed drug is withdrawn from sale for safety or effectiveness reasons, in accordance with the procedures in §314.161.

(c) An abbreviated new drug application described in paragraph (a) of this section will be disapproved, under §314.127(a)(11), and a 505(j)(2)(C) petition described in paragraph (a) of this section will be disapproved, under §314.93(e)(1)(iv), unless the agency determines that the withdrawal of the listed drug was not for safety or effectiveness reasons.

(d) Certain drug products approved for safety and effectiveness that were no longer marketed on September 24, 1984, are not included in the list. Any person who wishes to obtain marketing approval for such a drug product under an abbreviated new drug application must petition FDA for a determination whether the drug product was withdrawn from the market for safety or effectiveness reasons and request that the list be amended to include the drug product. A person seeking such a determination shall use the petition procedures established in §10.30 of this chapter. The petitioner shall include in the petition information to show that the drug product was approved for safety and effectiveness and all evidence available to the petitioner concerning the reason that marketing of the drug product ceased.

[57 FR 17990, Apr. 28, 1992; 57 FR 29353, July 1, 1992]
§314.125 Refusal to approve an application.

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

(1) FDA sends the applicant an approvable or a not approvable letter under §314.110 or §314.120;

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

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

(b) FDA may refuse to approve an application for any of the following reasons:

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

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

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

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

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

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

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

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

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

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

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

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

(13) The methods to be used in, and the facilities and controls used for, the manufacture, processing, packing, or holding of the drug substance or the drug product are inadequate to preserve its identity, strength, quality, purity, stability, and bioavailability.
product do not comply with the current good manufacturing practice regulations in parts 210 and 211.

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

(15) A nonclinical laboratory study that is described in the application and that is essential to show that the drug is safe for use under the conditions prescribed, recommended, or suggested in its proposed labeling was not conducted in compliance with the good laboratory practice regulations in part 58 of this chapter and no reason for the noncompliance is provided or, if it is, the differences between the practices used in conducting the study and the good laboratory practice regulations do not support the validity of the study.

(16) Any clinical investigation involving human subjects described in the application, subject to the institutional review board regulations in part 58 of this chapter or informed consent regulations in part 50 of this chapter, was not conducted in compliance with those regulations such that the rights or safety of human subjects were not adequately protected.

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

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

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


§314.126 Adequate and well-controlled studies.

(a) The purpose of conducting clinical investigations of a drug is to distinguish the effect of a drug from other influences, such as spontaneous change in the course of the disease, placebo effect, or biased observation. The characteristics described in paragraph (b) of this section have been developed over a period of years and are recognized by the scientific community as the essentials of an adequate and well-controlled clinical investigation. The Food and Drug Administration considers these characteristics in determining whether an investigation is adequate and well-controlled for purposes of section 505 of the act. Reports of adequate and well-controlled investigations provide the primary basis for determining whether there is “substantial evidence” to support the claims of effectiveness for new drugs. Therefore, the study report should provide sufficient details of study design, conduct,
and analysis to allow critical evaluation and a determination of whether the characteristics of an adequate and well-controlled study are present.

(b) An adequate and well-controlled study has the following characteristics:

1. There is a clear statement of the objectives of the investigation and a summary of the proposed or actual methods of analysis in the protocol for the study and in the report of its results. In addition, the protocol should contain a description of the proposed methods of analysis, and the study report should contain a description of the methods of analysis ultimately used. If the protocol does not contain a description of the proposed methods of analysis, the study report should describe how the methods used were selected.

2. The study uses a design that permits a valid comparison with a control to provide a quantitative assessment of drug effect. The protocol for the study and report of results should describe the study design precisely; for example, duration of treatment periods, whether treatments are parallel, sequential, or crossover, and whether the sample size is predetermined or based upon some interim analysis. Generally, the following types of control are recognized:

   (i) Placebo concurrent control. The test drug is compared with an inactive preparation designed to resemble the test drug as far as possible. A placebo-controlled study may include additional treatment groups, such as an active treatment control or a dose-comparison control, and usually includes randomization and blinding of patients or investigators, or both.

   (ii) Dose-comparison concurrent control. At least two doses of the drug are compared. A dose-comparison study may include additional treatment groups, such as placebo control or active control. Dose-comparison trials usually include randomization and blinding of patients or investigators, or both.

   (iii) No treatment concurrent control. Where objective measurements of effectiveness are available and placebo effect is negligible, the test drug is compared with no treatment. No treatment concurrent control trials usually include randomization.

   (iv) Active treatment concurrent control. The test drug is compared with known effective therapy; for example, where the condition treated is such that administration of placebo or no treatment would be contrary to the interest of the patient. An active treatment study may include additional treatment groups, however, such as a placebo control or a dose-comparison control. Active treatment trials usually include randomization and blinding of patients or investigators, or both. If the intent of the trial is to show similarity of the test and control drugs, the report of the study should assess the ability of the study to have detected a difference between treatments. Similarity of test drug and active control can mean either that both drugs were effective or that neither was effective. The analysis of the study should explain why the drugs should be considered effective in the study, for example, by reference to results in previous placebo-controlled studies of the active control drug.

   (v) Historical control. The results of treatment with the test drug are compared with experience historically derived from the adequately documented
natural history of the disease or condition, or from the results of active
treatment, in comparable patients or populations. Because historical
control populations usually cannot be as well assessed with respect to
pertinent variables as can concurrent control populations, historical control
designs are usually reserved for special circumstances. Examples include
studies of diseases with high and predictable mortality (for example,
certain malignancies) and studies in which the effect of the drug is self-
evident (general anesthetics, drug metabolism).

(3) The method of selection of subjects provides adequate assurance that they have
the disease or condition being studied, or evidence of susceptibility and
exposure to the condition against which prophylaxis is directed.

(4) The method of assigning patients to treatment and control groups minimizes bias
and is intended to assure comparability of the groups with respect to pertinent
variables such as age, sex, severity of disease, duration of disease, and use of
drugs or therapy other than the test drug. The protocol for the study and the
report of its results should describe how subjects were assigned to groups.
Ordinarily, in a concurrently controlled study, assignment is by randomization,
with or without stratification.

(5) Adequate measures are taken to minimize bias on the part of the subjects,
observers, and analysts of the data. The protocol and report of the study should
describe the procedures used to accomplish this, such as blinding.

(6) The methods of assessment of subjects' response are well-defined and reliable.
The protocol for the study and the report of results should explain the variables
measured, the methods of observation, and criteria used to assess response.

(7) There is an analysis of the results of the study adequate to assess the effects of the
drug. The report of the study should describe the results and the analytic
methods used to evaluate them, including any appropriate statistical methods.
The analysis should assess, among other things, the comparability of test and
control groups with respect to pertinent variables, and the effects of any interim
data analyses performed.

(c) The Director of the Center for Drug Evaluation and Research may, on the Director's
own initiative or on the petition of an interested person, waive in whole or in part any
of the criteria in paragraph (b) of this section with respect to a specific clinical
investigation, either prior to the investigation or in the evaluation of a completed
study. A petition for a waiver is required to set forth clearly and concisely the specific
criteria from which waiver is sought, why the criteria are not reasonably applicable to
the particular clinical investigation, what alternative procedures, if any, are to be, or
have been employed, and what results have been obtained. The petition is also
required to state why the clinical investigations so conducted will yield, or have
yielded, substantial evidence of effectiveness, notwithstanding nonconformance with
the criteria for which waiver is requested.

(d) For an investigation to be considered adequate for approval of a new drug, it is
required that the test drug be standardized as to identity, strength, quality, purity, and
dosage form to give significance to the results of the investigation.

(e) Uncontrolled studies or partially controlled studies are not acceptable as the sole basis
for the approval of claims of effectiveness. Such studies carefully conducted and
documented, may provide corroborative support of well-controlled studies regarding efficacy and may yield valuable data regarding safety of the test drug. Such studies will be considered on their merits in the light of the principles listed here, with the exception of the requirement for the comparison of the treated subjects with controls. Isolated case reports, random experience, and reports lacking the details which permit scientific evaluation will not be considered.


§314.127 Refusal to approve an abbreviated new drug application.
(a) FDA will refuse to approve an abbreviated application for a new drug under section 505(j) of the act for any of the following reasons:

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

(2) Information submitted with the abbreviated new drug application is insufficient to show that each of the proposed conditions of use has been previously approved for the listed drug referred to in the application.

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

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

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

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

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

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

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

(4)

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

(ii) If the abbreviated new drug application is for a drug product whose route of administration, dosage form, or strength is different from that of the listed

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drug referred to in the application, no petition to submit an abbreviated new drug application for the drug product with the different route of administration, dosage form, or strength was approved under §314.93.

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

(6)

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

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

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

(8)

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

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

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

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

1. A change in an inactive ingredient so that the product does not comply with an official compendium.
2. A change in composition to include an inactive ingredient that has not been previously approved in a drug product for human use by the same route of administration.
3. A change in the composition of a parenteral drug product to include an inactive ingredient that has not been previously approved in a parenteral drug product.
4. A change in composition of a drug product for ophthalmic use to include an inactive ingredient that has not been previously approved in a drug for ophthalmic use.
5. The use of a delivery or a modified release mechanism never before approved for the drug.
6. A change in composition to include a significantly greater content of one or more inactive ingredients than previously used in the drug product.
7. If the drug product is intended for topical administration, a change in the properties of the vehicle or base that might increase absorption of certain potentially toxic active ingredients thereby affecting the safety of the drug product, or a change in the lipophilic properties of a vehicle or base, e.g., a change from an oleaginous to a water soluble vehicle or base.

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

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

(9) Approval of the listed drug referred to in the abbreviated new drug application has been withdrawn or suspended for grounds described in §314.150(a) or FDA has published a notice of opportunity for hearing to withdraw approval of the reference listed drug under §314.150(a).

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

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

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

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

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

[57 FR 17991, Apr. 28, 1992; 57 FR 29353, July 1, 1992, as amended at 58 FR 25927, Apr. 28, 1993]

§314.150 Withdrawal of approval of an application or abbreviated application.

(a) The Food and Drug Administration will notify the applicant, and, if appropriate, all other persons who manufacture or distribute identical, related, or similar drug products as defined in §§310.6 and 314.151(a) of this chapter and for a new drug afford an opportunity for a hearing on a proposal to withdraw approval of the application or abbreviated new drug application under section 505(e) of the act and under the procedure in §314.200, if any of the following apply:

(1) The Secretary of Health Services has suspended the approval of the application or abbreviated application for a new drug on a finding that there is an imminent hazard to the public health. FDA will promptly afford the applicant an expedited hearing following summary suspension on a finding of imminent hazard to health.

(2) FDA finds:
(i) That clinical or other experience, tests, or other scientific data show that the drug is unsafe for use under the conditions of use upon the basis of which the application or abbreviated application was approved; or

(ii) That new evidence of clinical experience, not contained in the application or not available to FDA until after the application or abbreviated application was approved, or tests by new methods, or tests by methods not deemed reasonably applicable when the application or abbreviated application was approved, evaluated together with the evidence available when the application or abbreviated application was approved, reveal that the drug is not shown to be safe for use under the conditions of use upon the basis of which the application or abbreviated application was approved; or

(iii) Upon the basis of new information before FDA with respect to the drug, evaluated together with the evidence available when the application or abbreviated application was approved, that there is a lack of substantial evidence from adequate and well-controlled investigations as defined in §314.126, that the drug will have the effect it is purported or represented to have under the conditions of use prescribed, recommended, or suggested in its labeling; or

(iv) That the application or abbreviated application contains any untrue statement of a material fact; or

(v) That the patent information prescribed by section 505(c) of the act was not submitted within 30 days after the receipt of written notice from FDA specifying the failure to submit such information; or

(b) FDA may notify the applicant, and, if appropriate, all other persons who manufacture or distribute identical, related, or similar drug products as defined in §310.6, and for a new drug afford an opportunity for a hearing on a proposal to withdraw approval of the application or abbreviated new drug application under section 505(e) of the act and under the procedure in §314.200, if the agency finds:

1. That the applicant has failed to establish a system for maintaining required records, or has repeatedly or deliberately failed to maintain required records or to make required reports under section 505(k) or 507(g) of the act and §314.80, §314.81, or §314.98, or that the applicant has refused to permit access to, or copying or verification of, its records.

2. That on the basis of new information before FDA, evaluated together with the evidence available when the application or abbreviated application was approved, the methods used in, or the facilities and controls used for, the manufacture, processing, and packing of the drug are inadequate to ensure and preserve its identity, strength, quality, and purity and were not made adequate within a reasonable time after receipt of written notice from the agency.

3. That on the basis of new information before FDA, evaluated together with the evidence available when the application or abbreviated application was approved, the labeling of the drug, based on a fair evaluation of all material facts, is false or misleading in any particular, and the labeling was not corrected by the applicant within a reasonable time after receipt of written notice from the agency.
(4) That the applicant has failed to comply with the notice requirements of section 510(j)(2) of the act.

(5) That the applicant has failed to submit bioavailability or bioequivalence data required under part 320 of this chapter.

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

(7) That any nonclinical laboratory study that is described in the application or abbreviated application and that is essential to show that the drug is safe for use under the conditions prescribed, recommended, or suggested in its labeling was not conducted in compliance with the good laboratory practice regulations in part 58 of this chapter and no reason for the noncompliance was provided or, if it was, the differences between the practices used in conducting the study and the good laboratory practice regulations do not support the validity of the study.

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

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

(10) That the labeling for the drug product that is the subject of the abbreviated new drug application is no longer consistent with that for the listed drug referred to in the abbreviated new drug application, except for differences approved in the abbreviated new drug application or those differences resulting from:

   (i) A patent on the listed drug issued after approval of the abbreviated new drug application; or

   (ii) Exclusivity accorded to the listed drug after approval of the abbreviated new drug application that do not render the drug product less safe or effective than the listed drug for any remaining, nonprotected condition(s) of use.

(c) FDA will withdraw approval of an application or abbreviated application if the applicant requests its withdrawal because the drug subject to the application or abbreviated application is no longer being marketed, provided none of the conditions listed in paragraphs (a) and (b) of this section applies to the drug. FDA will consider a written request for a withdrawal under this paragraph to be a waiver of an opportunity for hearing otherwise provided for in this section. Withdrawal of approval of an application or abbreviated application under this paragraph is without prejudice to refiling.
(d) FDA may notify an applicant that it believes a potential problem associated with a drug is sufficiently serious that the drug should be removed from the market and may ask the applicant to waive the opportunity for hearing otherwise provided for under this section, to permit FDA to withdraw approval of the application or abbreviated application for the product, and to remove voluntarily the product from the market. If the applicant agrees, the agency will not make a finding under paragraph (b) of this section, but will withdraw approval of the application or abbreviated application in a notice published in the Federal Register that contains a brief summary of the agency's and the applicant's views of the reasons for withdrawal.


§314.151 Withdrawal of approval of an abbreviated new drug application under section 505(j)(5) of the act.

(a) Approval of an abbreviated new drug application approved under §314.105(d) may be withdrawn when the agency withdraws approval, under §314.150(a) or under this section, of the approved drug referred to in the abbreviated new drug application. If the agency proposed to withdraw approval of a listed drug under §314.150(a), the holder of an approved application for the listed drug has a right to notice and opportunity for hearing. The published notice of opportunity for hearing will identify all drug products approved under §314.105(d) whose applications are subject to withdrawal under this section if the listed drug is withdrawn, and will propose to withdraw such drugs. Holders of approved applications for the identified drug products will be provided notice and an opportunity to respond to the proposed withdrawal of their applications as described in paragraphs (b) and (c) of this section.

(b)(1) The published notice of opportunity for hearing on the withdrawal of the listed drug will serve as notice to holders of identified abbreviated new drug applications of the grounds for the proposed withdrawal.

(2) Holders of applications for drug products identified in the notice of opportunity for hearing may submit written comments on the notice of opportunity for hearing issued on the proposed withdrawal of the listed drug. If an abbreviated new drug application holder submits comments on the notice of opportunity for hearing and a hearing is granted, the abbreviated new drug application holder may participate in the hearing as a nonparty participant as provided for in §12.89 of this chapter.

(3) Except as provided in paragraphs (c) and (d) of this section, the approval of an abbreviated new drug application for a drug product identified in the notice of opportunity for hearing on the withdrawal of a listed drug will be withdrawn when the agency has completed the withdrawal of approval of the listed drug.

(c)

(1) If the holder of an application for a drug identified in the notice of opportunity for hearing has submitted timely comments but does not have an opportunity to participate in a hearing because a hearing is not requested or is settled, the submitted comments will be considered by the agency, which will issue an initial decision. The initial decision will respond to the comments, and contain the agency's decision whether there are grounds to withdraw approval of the listed drug and of the abbreviated new drug applications on which timely
comments were submitted. The initial decision will be sent to each abbreviated
new drug application holder that has submitted comments.

(2) Abbreviated new drug application holders to whom the initial decision was sent
may, within 30 days of the issuance of the initial decision, submit written
objections.

(3) The agency may, at its discretion, hold a limited oral hearing to resolve dispositive
factual issues that cannot be resolved on the basis of written submissions.

(4) If there are no timely objections to the initial decision, it will become final at the
expiration of 30 days.

(5) If timely objections are submitted, they will be reviewed and responded to in a
final decision.

(6) The written comments received, the initial decision, the evidence relied on in the
comments and in the initial decision, the objections to the initial decision, and,
if a limited oral hearing has been held, the transcript of that hearing and any
documents submitted therein, shall form the record upon which the agency shall
make a final decision.

(7) Except as provided in paragraph (d) of this section, any abbreviated new drug
application whose holder submitted comments on the notice of opportunity for
hearing shall be withdrawn upon the issuance of a final decision concluding that
the listed drug should be withdrawn for grounds as described in §314.150(a).
The final decision shall be in writing and shall constitute final agency action,
reviewable in a judicial proceeding.

(8) Documents in the record will be publicly available in accordance with §10.20(j) of
this chapter. Documents available for examination or copying will be placed on
public display in the Dockets Management Branch (HFA-305), Food and Drug
Administration, room 1-23, 12420 Parklawn Dr., Rockville, MD 20857,
promptly upon receipt in that office.

(d) If the agency determines, based upon information submitted by the holder of an
abbreviated new drug application, that the grounds for withdrawal of the listed drug
are not applicable to a drug identified in the notice of opportunity for hearing, the
final decision will state that the approval of the abbreviated new drug application for
such drug is not withdrawn.

[57 FR 17994, Apr. 28, 1992]

§314.152 Notice of withdrawal of approval of an application or
abbreviated application for a new drug.

If the Food and Drug Administration withdraws approval of an application or abbreviated
application for a new drug, FDA will publish a notice in the Federal Register announcing
the withdrawal of approval. If the application or abbreviated application was withdrawn
for grounds described in §314.150(a) or §314.151, the notice will announce the removal
of the drug from the list of approved drugs published under section 505(j)(6) of the act
and shall satisfy the requirement of §314.162(b).

[57 FR 17994, Apr. 28, 1992]
§314.153 Suspension of approval of an abbreviated new drug application.

(a) Suspension of approval. The approval of an abbreviated new drug application approved under §314.105(d) shall be suspended for the period stated when:

1. The Secretary of the Department of Health Services, under the imminent hazard authority of section 505(e) of the act or the authority of this paragraph, suspends approval of a listed drug referred to in the abbreviated new drug application, for the period of the suspension;
2. The agency, in the notice described in paragraph (b) of this section, or in any subsequent written notice given an abbreviated new drug application holder by the agency, concludes that the risk of continued marketing and use of the drug is inappropriate, pending completion of proceedings to withdraw or suspend approval under §314.151 or paragraph (b) of this section; or
3. The agency, under the procedures set forth in paragraph (b) of this section, issues a final decision stating the determination that the abbreviated application is suspended because the listed drug on which the approval of the abbreviated new drug application depends has been withdrawn from sale for reasons of safety or effectiveness or has been suspended under paragraph (b) of this section. The suspension will take effect on the date stated in the decision and will remain in effect until the agency determines that the marketing of the drug has resumed or that the withdrawal is not for safety or effectiveness reasons.

(b) Procedures for suspension of abbreviated new drug applications when a listed drug is voluntarily withdrawn for safety or effectiveness reasons.

1. If a listed drug is voluntarily withdrawn from sale, and the agency determines that the withdrawal from sale was for reasons of safety or effectiveness, the agency will send each holder of an approved abbreviated new drug application that is subject to suspension as a result of this determination a copy of the agency's initial decision setting forth the reasons for the determination. The initial decision will also be placed on file with the Dockets Management Branch (HFA-305), Food and Drug Administration, room 1-23, 12420 Parklawn Dr., Rockville, MD 20857.

2. Each abbreviated new drug application holder will have 30 days from the issuance of the initial decision to present, in writing, comments and information bearing on the initial decision. If no comments or information is received, the initial decision will become final at the expiration of 30 days.

3. Comments and information received within 30 days of the issuance of the initial decision will be considered by the agency and responded to in a final decision.

4. The agency may, in its discretion, hold a limited oral hearing to resolve dispositive factual issues that cannot be resolved on the basis of written submissions.

5. If the final decision affirms the agency's initial decision that the listed drug was withdrawn for reasons of safety or effectiveness, the decision will be published in the Federal Register in compliance with §314.152, and will, except as provided in paragraph (b)(6) of this section, suspend approval of all abbreviated new drug applications identified under paragraph (b)(1) of this section and remove from the list the listed drug and any drug whose approval was
suspended under this paragraph. The notice will satisfy the requirement of §314.162(b). The agency's final decision and copies of materials on which it relies will also be filed with the Dockets Management Branch (address in paragraph (b)(1) of this section).

(6) If the agency determines in its final decision that the listed drug was withdrawn for reasons of safety or effectiveness but, based upon information submitted by the holder of an abbreviated new drug application, also determines that the reasons for the withdrawal of the listed drug are not relevant to the safety and effectiveness of the drug subject to such abbreviated new drug application, the final decision will state that the approval of such abbreviated new drug application is not suspended.

(7) Documents in the record will be publicly available in accordance with §10.20(j) of this chapter. Documents available for examination or copying will be placed on public display in the Dockets Management Branch (address in paragraph (b)(1) of this section) promptly upon receipt in that office.

[57 FR 17995, Apr. 28, 1992]

§314.160 Approval of an application or abbreviated application for which approval was previously refused, suspended, or withdrawn.

Upon the Food and Drug Administration's own initiative or upon request of an applicant, FDA may, on the basis of new data, approve an application or abbreviated application which it had previously refused, suspended, or withdrawn approval. FDA will publish a notice in the Federal Register announcing the approval.

[57 FR 17995, Apr. 28, 1992]

§314.161 Determination of reasons for voluntary withdrawal of a listed drug.

(a) A determination whether a listed drug that has been voluntarily withdrawn from sale was withdrawn for safety or effectiveness reasons may be made by the agency at any time after the drug has been voluntarily withdrawn from sale, but must be made:

(1) Prior to approving an abbreviated new drug application that refers to the listed drug;

(2) Whenever a listed drug is voluntarily withdrawn from sale and abbreviated new drug applications that referred to the listed drug have been approved; and

(3) When a person petitions for such a determination under §§10.25(a) and 10.30 of this chapter.

(b) Any person may petition under §§10.25(a) and 10.30 of this chapter for a determination whether a listed drug has been voluntarily withdrawn for safety or effectiveness reasons. Any such petition must contain all evidence available to the petitioner concerning the reason that the drug is withdrawn from sale.

(c) If the agency determines that a listed drug is withdrawn from sale for safety or effectiveness reasons, the agency will, except as provided in paragraph (d) of this section, publish a notice of the determination in the Federal Register.

(d) If the agency determines under paragraph (a) of this section that a listed drug is withdrawn from sale for safety and effectiveness reasons and there are approved
abbreviated new drug applications that are subject to suspension under section 505(j)(5) of the act, FDA will initiate a proceeding in accordance with §314.153(b).

(e) A drug that the agency determines is withdrawn for safety or effectiveness reasons will be removed from the list, under §314.162. The drug may be relisted if the agency has evidence that marketing of the drug has resumed or that the withdrawal is not for safety or effectiveness reasons. A determination that the drug is not withdrawn for safety or effectiveness reasons may be made at any time after its removal from the list, upon the agency's initiative, or upon the submission of a petition under §§10.25(a) and 10.30 of this chapter. If the agency determines that the drug is not withdrawn for safety or effectiveness reasons, the agency shall publish a notice of this determination in the Federal Register. The notice will also announce that the drug is relisted, under §314.162(c). The notice will also serve to reinstate approval of all suspended abbreviated new drug applications that referred to the listed drug.

[57 FR 17995, Apr. 28, 1992]

§314.162 Removal of a drug product from the list.

(a) FDA will remove a previously approved new drug product from the list for the period stated when:

(1) The agency withdraws or suspends approval of a new drug application or an abbreviated new drug application under §314.150(a) or §314.151 or under the imminent hazard authority of section 505(e) of the act, for the same period as the withdrawal or suspension of the application; or

(2) The agency, in accordance with the procedures in §314.153(b) or §314.161, issues a final decision stating that the listed drug was withdrawn from sale for safety or effectiveness reasons, or suspended under §314.153(b), until the agency determines that the withdrawal from the market has ceased or is not for safety or effectiveness reasons.

(b) FDA will publish in the Federal Register a notice announcing the removal of a drug from the list.

(c) At the end of the period specified in paragraph (a)(1) or (a)(2) of this section, FDA will relist a drug that has been removed from the list. The agency will publish in the Federal Register a notice announcing the relisting of the drug.

[57 FR 17996, Apr. 28, 1992]

§314.170 Adulteration and misbranding of an approved drug.

All drugs, including those the Food and Drug Administration approves under section 505 of the act and this part, are subject to the adulteration and misbranding provisions in sections 501, 502, and 503 of the act. FDA is authorized to regulate approved new drugs by regulations issued through informal rulemaking under sections 501, 502, and 503 of the act.

Subpart E--Hearing Procedures for New Drugs

§314.200 Notice of opportunity for hearing; notice of participation and request for hearing; grant or denial of hearing.


(a) Notice of opportunity for hearing. The Director of the Center for Drug Evaluation and Research, Food and Drug Administration, will give the applicant, and all other persons who manufacture or distribute identical, related, or similar drug products as defined in §310.6 of this chapter, notice and an opportunity for a hearing on the Center's proposal to refuse to approve an application or to withdraw the approval of an application or abbreviated application under section 505(e) of the act. The notice will state the reasons for the action and the proposed grounds for the order.

(1) The notice may be general (that is, simply summarizing in a general way the information resulting in the notice) or specific (that is, either referring to specific requirements in the statute and regulations with which there is a lack of compliance, or providing a detailed description and analysis of the specific facts resulting in the notice).

(2) FDA will publish the notice in the Federal Register and will state that the applicant, and other persons subject to the notice under §310.6, who wishes to participate in a hearing, has 30 days after the date of publication of the notice to file a written notice of participation and request for hearing. The applicant, or other persons subject to the notice under §310.6, who fails to file a written notice of participation and request for hearing within 30 days, waives the opportunity for a hearing.

(3) It is the responsibility of every manufacturer and distributor of a drug product to review every notice of opportunity for a hearing published in the Federal Register to determine whether it covers any drug product that person manufactures or distributes. Any person may request an opinion of the applicability of a notice to a specific product that may be identical, related, or similar to a product listed in a notice by writing to the Division of Drug Labeling Compliance (HFD- 310), Center for Drug Evaluation and Research, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857. A person shall request an opinion within 30 days of the date of publication of the notice to be eligible for an opportunity for a hearing under the notice. If a person requests an opinion, that person's time for filing an appearance and request for a hearing and supporting studies and analyses begins on the date the person receives the opinion from FDA.

(b) FDA will provide the notice of opportunity for a hearing to applicants and to other persons subject to the notice under §310.6, as follows:

(1) To any person who has submitted an application or abbreviated application, by delivering the notice in person or by sending it by registered or certified mail to the last address shown in the application or abbreviated application.

(2) To any person who has not submitted an application or abbreviated application but who is subject to the notice under §310.6 of this chapter, by publication of the notice in the Federal Register.
(c) Notice of participation and request for a hearing, and submission of studies and comments. The applicant, or any other person subject to the notice under §310.6, who wishes to participate in a hearing, shall file with the Dockets Management Branch (HFA-305), Food and Drug Administration, rm. 1-23, 12420 Parklawn Dr., Rockville, MD 20857,

(i) within 30 days after the date of the publication of the notice (or of the date of receipt of an opinion requested under paragraph (a)(3) of this section) a written notice of participation and request for a hearing and

(ii) within 60 days after the date of publication of the notice, unless a different period of time is specified in the notice of opportunity for a hearing, the studies on which the person relies to justify a hearing as specified in paragraph (d) of this section. The applicant, or other person, may incorporate by reference the raw data underlying a study if the data were previously submitted to FDA as part of an application, abbreviated application, or other report.

(2) FDA will not consider data or analyses submitted after 60 days in determining whether a hearing is warranted unless they are derived from well-controlled studies begun before the date of the notice of opportunity for hearing and the results of the studies were not available within 60 days after the date of publication of the notice. Nevertheless, FDA may consider other studies on the basis of a showing by the person requesting a hearing of inadvertent omission and hardship. The person requesting a hearing shall list in the request for hearing all studies in progress, the results of which the person intends later to submit in support of the request for a hearing. The person shall submit under paragraph (c)(1)(ii) of this section a copy of the complete protocol, a list of the participating investigators, and a brief status report of the studies.

(3) Any other interested person who is not subject to the notice of opportunity for a hearing may also submit comments on the proposal to withdraw approval of the application or abbreviated application. The comments are requested to be submitted within the time and under the conditions specified in this section.

(d) The person requesting a hearing is required to submit under paragraph (c)(1)(ii) of this section the studies (including all protocols and underlying raw data) on which the person relies to justify a hearing with respect to the drug product. Except, a person who requests a hearing on the refusal to approve an application is not required to submit additional studies and analyses if the studies upon which the person relies have been submitted in the application and in the format and containing the summaries required under §314.50.

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

(2) The submission is required to include a factual analysis of all the studies submitted. If the grounds for FDA's proposed action concern the effectiveness of the drug, the analysis is required to specify how each study accords, on a point-by-point basis, with each criterion required for an adequate well-controlled clinical investigation established under §314.126 and, if the product is a combination drug product, with each of the requirements for a combination drug established in §300.50, or the study is required to be accompanied by an appropriate waiver previously granted by FDA. If a study concerns a drug or dosage form or condition of use or mode of administration other than the one in question, that fact is required to be clearly stated. Any study conducted on the final marketed form of the drug product is required to be clearly identified.

(3) Each person requesting a hearing shall submit an analysis of the data upon which the person relies, except that the required information relating either to safety or to effectiveness may be omitted if the notice of opportunity for hearing does not raise any issue with respect to that aspect of the drug; information on compliance with §300.50 may be omitted if the drug product is not a combination drug product. A financial certification or disclosure statement or both as required by part 54 of this chapter must accompany all clinical data submitted. FDA can most efficiently consider submissions made in the following format.

I. Safety data.
   A. Animal safety data.
      1. Individual active components.
         a. Controlled studies.
         b. Partially controlled or uncontrolled studies.
      2. Combinations of the individual active components.
         a. Controlled studies.
         b. Partially controlled or uncontrolled studies.
   B. Human safety data.
      1. Individual active components.
         a. Controlled studies.
         b. Partially controlled or uncontrolled studies.
         c. Documented case reports.
         d. Pertinent marketing experiences that may influence a
determination about the safety of each individual active
cOMPONENT.
      2. Combinations of the individual active components.
         a. Controlled studies.
         b. Partially controlled or uncontrolled studies.
         c. Documented case reports.
         d. Pertinent marketing experiences that may influence a
determination about the safety of each individual active
cOMPONENT.

II. Effectiveness data.
A. Individual active components: Controlled studies, with an analysis showing clearly how each study satisfies, on a point-by-point basis, each of the criteria required by §314.126.

B. Combinations of individual active components.
   1. Controlled studies with an analysis showing clearly how each study satisfies on a point-by-point basis, each of the criteria required by §314.126.
   2. An analysis showing clearly how each requirement of §300.50 has been satisfied.

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

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

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

(e) Contentions that a drug product is not subject to the new drug requirements. A notice of opportunity for a hearing encompasses all issues relating to the legal status of each drug product subject to it, including identical, related, and similar drug products as defined in §310.6. A notice of appearance and request for a hearing under paragraph (c)(1)(i) of this section is required to contain any contention that the product is not a new drug because it is generally recognized as safe and effective within the meaning of section 201(p) of the act, or because it is exempt from part or all of the new drug provisions of the act under the exemption for products marketed before June 25, 1938, contained in section 201(p) of the act or under section 107(c) of the Drug Amendments of 1962, or for any other reason. Each contention is required to be supported by a submission under paragraph (c)(1)(ii) of this section and the Commissioner of Food and Drugs will make an administrative determination on each contention. The failure of any person subject to a notice of opportunity for a hearing, including any person who manufactures or distributes an identical, related, or similar drug product as defined in §310.6, to submit a notice of participation and request for hearing or to raise all such contentions constitutes a waiver of any contentions not raised.

(1) A contention that a drug product is generally recognized as safe and effective within the meaning of section 201(p) of the act is required to be supported by submission of the same quantity and quality of scientific evidence that is required to obtain approval of an application for the product, unless FDA has waived a requirement for effectiveness (under §314.126) or safety, or both. The submission should be in the format and with the analyses required under paragraph (d) of this section. A person who fails to submit the required scientific evidence required under paragraph (d) waives the contention. General
recognition of safety and effectiveness shall ordinarily be based upon published studies which may be corroborated by unpublished studies and other data and information.

(2) A contention that a drug product is exempt from part or all of the new drug provisions of the act under the exemption for products marketed before June 25, 1938, contained in section 201(p) of the act, or under section 107(c) of the Drug Amendments of 1962, is required to be supported by evidence of past and present quantitative formulas, labeling, and evidence of marketing. A person who makes such a contention should submit the formulas, labeling, and evidence of marketing in the following format.

I. Formulation.
   A. A copy of each pertinent document or record to establish the exact quantitative formulation of the drug (both active and inactive ingredients) on the date of initial marketing of the drug.
   B. A statement whether such formulation has at any subsequent time been changed in any manner. If any such change has been made, the exact date, nature, and rationale for each change in formulation, including any deletion or change in the concentration of any active ingredient and/or inactive ingredient, should be stated, together with a copy of each pertinent document or record to establish the date and nature of each such change, including, but not limited to, the formula which resulted from each such change. If no such change has been made, a copy of representative documents or records showing the formula at representative points in time should be submitted to support the statement.

II. Labeling.
   A. A copy of each pertinent document or record to establish the identity of each item of written, printed, or graphic matter used as labeling on the date the drug was initially marketed.
   B. A statement whether such labeling has at any subsequent time been discontinued or changed in any manner. If such discontinuance or change has been made, the exact date, nature, and rationale for each discontinuance or change and a copy of each pertinent document or record to establish each such discontinuance or change should be submitted, including, but not limited to, the labeling which resulted from each such discontinuance or change. If no such discontinuance or change has been made, a copy of representative documents or records showing labeling at representative points in time should be submitted to support the statement.

III. Marketing.
   A. A copy of each pertinent document or record to establish the exact date the drug was initially marketed.
   B. A statement whether such marketing has at any subsequent time been discontinued. If such marketing has been discontinued, the exact date of each such discontinuance should be submitted, together with a copy of each pertinent document or record to establish each such date.
IV. Verification. A statement signed by the person responsible for such submission, that all appropriate records have been searched and to the best of that person's knowledge and belief it includes a true and accurate presentation of the facts. (Warning: A willfully false statement is a criminal offense, 18 U.S.C. 1001.)

(3) The Food and Drug Administration will not find a drug product, including any active ingredient, which is identical, related, or similar, as described in §310.6, to a drug product, including any active ingredient for which an application is or at any time has been effective or deemed approved, or approved under section 505 of the act, to be exempt from part or all of the new drug provisions of the act.

(4) A contention that a drug product is not a new drug for any other reason is required to be supported by submission of the factual records, data, and information that are necessary and appropriate to support the contention.

(5) It is the responsibility of every person who manufactures or distributes a drug product in reliance upon a “grandfather” provision of the act to maintain files that contain the data and information necessary fully to document and support that status.

(f) Separation of functions. Separation of functions commences upon receipt of a request for hearing. The Director of the Center for Drug Evaluation and Research, Food and Drug Administration, will prepare an analysis of the request and a proposed order ruling on the matter. The analysis and proposed order, the request for hearing, and any proposed order denying a hearing and response under paragraph (g) (2) or (3) of this section will be submitted to the Office of the Commissioner of Food and Drugs for review and decision. When the Center for Drug Evaluation and Research recommends denial of a hearing on all issues on which a hearing is requested, no representative of the Center will participate or advise in the review and decision by the Commissioner. When the Center for Drug Evaluation and Research recommends that a hearing be granted on one or more issues on which a hearing is requested, separation of functions terminates as to those issues, and representatives of the Center may participate or advise in the review and decision by the Commissioner on those issues. The Commissioner may modify the text of the issues, but may not deny a hearing on those issues. Separation of functions continues with respect to issues on which the Center for Drug Evaluation and Research has recommended denial of a hearing. The Commissioner will neither evaluate nor rule on the Center's recommendation on such issues and such issues will not be included in the notice of hearing. Participants in the hearing may make a motion to the presiding officer for the inclusion of any such issue in the hearing. The ruling on such a motion is subject to review in accordance with §12.35(b). Failure to so move constitutes a waiver of the right to a hearing on such an issue. Separation of functions on all issues resumes upon issuance of a notice of hearing. The Office of the General Counsel, Department of Health Services, will observe the same separation of functions.

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

(2) When following a general notice of opportunity for a hearing (as defined in paragraph (a)(1) of this section) the Director of the Center for Drug Evaluation and Research concludes that summary judgment against a person requesting a hearing should be considered, the Director will serve upon the person requesting a hearing by registered mail a proposed order denying a hearing. This person has 60 days after receipt of the proposed order to respond with sufficient data, information, and analyses to demonstrate that there is a genuine and substantial issue of fact which justifies a hearing.

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

(4) If review of the data, information, and analyses submitted show that the grounds cited in the notice are not valid, for example, that substantial evidence of effectiveness exists, the Commissioner will enter summary judgment for the person requesting the hearing, and rescind the notice of opportunity for hearing.

(5) If the Commissioner grants a hearing, it will begin within 90 days after the expiration of the time for requesting the hearing unless the parties otherwise agree in the case of denial of approval, and as soon as practicable in the case of withdrawal of approval.

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

(7) If the manufacturer or distributor of an identical, related, or similar drug product requests and is granted a hearing, the hearing may consider whether the product
is in fact identical, related, or similar to the drug product named in the notice of opportunity for a hearing.

(8) A request for a hearing, and any subsequent grant or denial of a hearing, applies only to the drug products named in such documents.

(h) FDA will issue a notice withdrawing approval and declaring all products unlawful for drug products subject to a notice of opportunity for a hearing, including any identical, related, or similar drug product under §310.6, for which an opportunity for a hearing is waived or for which a hearing is denied. The Commissioner may defer or stay the action pending a ruling on any related request for a hearing or pending any related hearing or other administrative or judicial proceeding.


§314.201 Procedure for hearings. Parts 10 through 16 apply to hearings relating to new drugs under section 505 (d) and (e) of the act.

§314.235 Judicial review.

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

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

Subpart F [Reserved]

Subpart G--Miscellaneous Provisions

§314.410 Imports and exports of new drugs.


(a) Imports.

(1) A new drug may be imported into the United States if:

   (i) It is the subject of an approved application under this part; or

   (ii) it complies with the regulations pertaining to investigational new drugs under part 312; and it complies with the general regulations pertaining to imports under subpart E of part 1.

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

(b) Exports.

(1) A new drug may be exported if it is the subject of an approved application under this part or it complies with the regulations pertaining to investigational new drugs under part 312.

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

(3) Insulin or an antibiotic drug may be exported without regard to the requirements in section 802 of the act if the insulin or antibiotic drug meets the requirements of section 801(e)(1) of the act.

[50 FR 7493, Feb. 22, 1985, unless otherwise noted. Redesignated at 57 FR 17983, Apr. 28, 1992, and amended at 64 FR 402, Jan. 5, 1999]

§314.420 Drug master files.

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

(1) [Reserved]
(2) Drug substance, drug substance intermediate, and materials used in their preparation, or drug product;
(3) Packaging materials;
(4) Excipient, colorant, flavor, essence, or materials used in their preparation;
(5) FDA-accepted reference information. (A person wishing to submit information and supporting data in a drug master file (DMF) that is not covered by Types II through IV DMF's must first submit a letter of intent to the Drug Master File Staff, Food and Drug Administration, 12229 Wilkins Ave., Rockville, MD 20852). FDA will then contact the person to discuss the proposed submission.

(b) An investigational new drug application or an application, abbreviated application, amendment, or supplement may incorporate by reference all or part of the contents of any drug master file in support of the submission if the holder authorizes the incorporation in writing. Each incorporation by reference is required to describe the
incorporated material by name, reference number, volume, and page number of the drug master file.

(c) A drug master file is required to be submitted in two copies. The agency has prepared guidance that provides information about how to prepare a well-organized drug master file. If the drug master file holder adds, changes, or deletes any information in the file, the holder shall notify in writing, each person authorized to reference that information. Any addition, change, or deletion of information in a drug master file (except the list required under paragraph (d) of this section) is required to be submitted in two copies and to describe by name, reference number, volume, and page number the information affected in the drug master file.

(d) The drug master file is required to contain a complete list of each person currently authorized to incorporate by reference any information in the file, identifying by name, reference number, volume, and page number the information that each person is authorized to incorporate. If the holder restricts the authorization to particular drug products, the list is required to include the name of each drug product and the application number, if known, to which the authorization applies.

(e) The public availability of data and information in a drug master file, including the availability of data and information in the file to a person authorized to reference the file, is determined under part 20 and §314.430.


§314.430 Availability for public disclosure of data and information in an application or abbreviated application.

(a) The Food and Drug Administration will determine the public availability of any part of an application or abbreviated application under this section and part 20 of this chapter. For purposes of this section, the application or abbreviated application includes all data and information submitted with or incorporated by reference in the application or abbreviated application, including investigational new drug applications, drug master files under §314.420, supplements submitted under §314.70 or §314.97, reports under §314.80 or §314.98, and other submissions. For purposes of this section, safety and effectiveness data include all studies and tests of a drug on animals and all studies and tests of the drug for identity, stability, purity, potency, and bioavailability.

(b) FDA will not publicly disclose the existence of an application or abbreviated application before an approvable letter is sent to the applicant under §314.110, unless the existence of the application or abbreviated application has been previously publicly disclosed or acknowledged. The Center for Drug Evaluation and Research will maintain and make available for public disclosure a list of applications or abbreviated applications for which the agency has sent an approvable letter to the applicant.

(c) If the existence of an unapproved application or abbreviated application has not been publicly disclosed or acknowledged, no data or information in the application or abbreviated application is available for public disclosure.

(d)
(1) If the existence of an application or abbreviated application has been publicly disclosed or acknowledged before the agency sends an approval letter to the applicant, no data or information contained in the application or abbreviated application is available for public disclosure before the agency sends an approval letter, but the Commissioner may, in his or her discretion, disclose a summary of selected portions of the safety and effectiveness data that are appropriate for public consideration of a specific pending issue; for example, for consideration of an open session of an FDA advisory committee.

(2) Notwithstanding paragraph (d)(1) of this section, FDA will make available to the public upon request the information in the investigational new drug application that was required to be filed in Docket Number 95S-0158 in the Dockets Management Branch (HFA-305), Food and Drug Administration, 12420 Parklawn Dr., rm. 1-23, Rockville, MD 20857, for investigations involving an exception from informed consent under §50.24 of this chapter. Persons wishing to request this information shall submit a request under the Freedom of Information Act.

(e) After FDA sends an approval letter to the applicant, the following data and information in the application or abbreviated application are immediately available for public disclosure, unless the applicant shows that extraordinary circumstances exist. A list of approved applications and abbreviated applications is available from the Government Printing Office, Washington, DC 20402. This list is updated monthly.

(1) [Reserved]
(2) If the application applies to a new drug, all safety and effectiveness data previously disclosed to the public as set forth in §20.81 and a summary or summaries of the safety and effectiveness data and information submitted with or incorporated by reference in the application. The summaries do not constitute the full reports of investigations under section 505(b)(1) of the act (21 U.S.C. 355(b)(1)) on which the safety or effectiveness of the drug may be approved. The summaries consist of the following:
   (i) For an application approved before July 1, 1975, internal agency records that describe safety and effectiveness data and information, for example, a summary of the basis for approval or internal reviews of the data and information, after deletion of the following:
      (a) Names and any information that would identify patients or test subjects or investigators.
      (b) Any inappropriate gratuitous comments unnecessary to an objective analysis of the data and information.
   (ii) For an application approved on or after July 1, 1975, a Summary Basis of Approval (SBA) document that contains a summary of the safety and effectiveness data and information evaluated by FDA during the drug approval process. The SBA is prepared in one of the following ways:
      (a) Before approval of the application, the applicant may prepare a draft SBA which the Center for Drug Evaluation and Research will review
and may revise. The draft may be submitted with the application or as an amendment.

(b) The Center for Drug Evaluation and Research may prepare the SBA.

(3) A protocol for a test or study, unless it is shown to fall within the exemption established for trade secrets and confidential commercial information in §20.61.

(4) Adverse reaction reports, product experience reports, consumer complaints, and other similar data and information after deletion of the following:
   (i) Names and any information that would identify the person using the product.
   (ii) Names and any information that would identify any third party involved with the report, such as a physician or hospital or other institution.

(5) A list of all active ingredients and any inactive ingredients previously disclosed to the public as set forth in §20.81.

(6) An assay method or other analytical method, unless it serves no regulatory or compliance purpose and is shown to fall within the exemption established for trade secrets and confidential commercial information in §20.61.

(7) All correspondence and written summaries of oral discussions between FDA and the applicant relating to the application, under the provisions of part 20.

(f) All safety and effectiveness data and information which have been submitted in an application and which have not previously been disclosed to the public are available to the public, upon request, at the time any one of the following events occurs unless extraordinary circumstances are shown:
   (1) No work is being or will be undertaken to have the application approved.
   (2) A final determination is made that the application is not approvable and all legal appeals have been exhausted.
   (3) Approval of the application is withdrawn and all legal appeals have been exhausted.
   (4) A final determination has been made that the drug is not a new drug.
   (5) For applications submitted under section 505(b) of the act, the effective date of the approval of the first abbreviated application submitted under section 505(j) of the act which refers to such drug, or the date on which the approval of an abbreviated application under section 505(j) of the act which refers to such drug could be made effective if such an abbreviated application had been submitted.
   (6) For abbreviated applications submitted under section 505(j) of the act, when FDA sends an approval letter to the applicant.

(g) The following data and information in an application or abbreviated application are not available for public disclosure unless they have been previously disclosed to the public as set forth in §20.81 of this chapter or they relate to a product or ingredient that has been abandoned and they do not represent a trade secret or confidential commercial or financial information under §20.61 of this chapter:
   (1) Manufacturing methods or processes, including quality control procedures.
   (2) Production, sales distribution, and similar data and information, except that any compilation of that data and information aggregated and prepared in a way that does not reveal data or information which is not available for public disclosure under this provision is available for public disclosure.
   (3) Quantitative or semiquantitative formulas.
(h) The compilations of information specified in §20.117 are available for public disclosure.


§314.440 Addresses for applications and abbreviated applications.

(a) Applicants shall send applications, abbreviated applications, and other correspondence relating to matters covered by this part, except for products listed in paragraph (b) of this section, to the Center for Drug Evaluation and Research, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, and directed to the appropriate office identified below:

1. Except as provided in paragraph (a)(4) of this section, an application under §314.50 or §314.54 submitted for filing should be directed to the Document and Records Section, 12420 Parklawn Dr., Rockville, MD 20852. Applicants may obtain folders for binding applications from the Consolidated Forms and Publications Distribution Center, Washington Commerce Center, 3222 Hubbard Rd., Landover, MD 20785. After FDA has filed the application, the agency will inform the applicant which division is responsible for the application. Amendments, supplements, resubmissions, requests for waivers, and other correspondence about an application that has been filed should be directed to the appropriate division.

2. Except as provided in paragraph (a)(4) of this section, an abbreviated application under §314.94, and amendments, supplements, and resubmissions should be directed to the Office of Generic Drugs (HFD-600), Center for Drug Evaluation and Research, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857. Items sent by parcel post or overnight courier service should be directed to the Office of Generic Drugs (HFD-600), Center for Drug Evaluation and Research, Food and Drug Administration, Metro Park North II, 7500 Standish Place, rm. 150, Rockville, MD 20855. Correspondence not associated with an application should be addressed specifically to the intended office or division and to the person as follows: Center for Drug Evaluation and Research, Food and Drug Administration, Attn: [insert name of person], MPN II, HFD-[insert mail code of office or division], 5600 Fishers Lane, Rockville, MD 20857. The mail code for the Office of Generic Drugs is HFD-600, the mail code for the Division of Chemistry is HFD-630, and the mail code for the Division of Bioequivalence is HFD-650.

3. A request for an opportunity for a hearing under §314.110 or §314.120 on the question of whether there are grounds for denying approval of an application, except an application under paragraph (b) of this section, should be directed to the Associate Director for Policy (HFD-5).

4. The field copy of an application, an abbreviated application, amendments, supplements, resubmissions, requests for waivers, and other correspondence about an application and an abbreviated application shall be sent to the applicant's home FDA district office, except that a foreign applicant shall send
the field copy to the appropriate address identified in paragraphs (a)(1) and (a)(2) of this section.

(b) Applicants shall send applications and other correspondence relating to matters covered by this part for the drug products listed below to the Division of Product Certification (HFB-240), Center for Biologics Evaluation and Research, Food and Drug Administration, 8800 Rockville Pike, Bethesda, MD 20892, except applicants shall send a request for an opportunity for a hearing under §314.110 or §314.120 on the question of whether there are grounds for denying approval of an application to the Director, Center for Biologics Evaluation and Research (HFB-1), at the same address.

(1) Ingredients packaged together with containers intended for the collection, processing, or storage of blood and blood components.

(2) Urokinase products.

(3) Plasma volume expanders and hydroxyethyl starch for leukapheresis.

§314.445 Guidance documents.

(a) FDA has made available guidance documents under §10.115 of this chapter to help you to comply with certain requirements of this part.

(b) The Center for Drug Evaluation and Research (CDER) maintains a list of guidance documents that apply to CDER’s regulations. The list is maintained on the Internet and is published annually in the Federal Register. A request for a copy of the CDER list should be directed to the Office of Training and Communications, Division of Communications Management, Drug Information Branch (HFD-210), Center for Drug Evaluation and Research, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857.

[65 FR 56480, Sept. 19, 2000]

Subpart H--Accelerated Approval of New Drugs for Serious or Life-Threatening Illnesses

§314.500 Scope.

Source: 57 FR 58958, Dec. 11, 1992, unless otherwise noted.

This subpart applies to certain new drug products that have been studied for their safety and effectiveness in treating serious or life-threatening illnesses and that provide meaningful therapeutic benefit to patients over existing treatments (e.g., ability to treat patients unresponsive to, or intolerant of, available therapy, or improved patient response over available therapy).

[57 FR 58958, Dec. 11, 1992, as amended at 64 FR 402, Jan. 5, 1999]
§314.510 Approval based on a surrogate endpoint or on an effect on a clinical endpoint other than survival or irreversible morbidity.

FDA may grant marketing approval for a new drug product on the basis of adequate and well-controlled clinical trials establishing that the drug product has an effect on a surrogate endpoint that is reasonably likely, based on epidemiologic, therapeutic, pathophysiologic, or other evidence, to predict clinical benefit or on the basis of an effect on a clinical endpoint other than survival or irreversible morbidity. Approval under this section will be subject to the requirement that the applicant study the drug further, to verify and describe its clinical benefit, where there is uncertainty as to the relation of the surrogate endpoint to clinical benefit, or of the observed clinical benefit to ultimate outcome. Postmarketing studies would usually be studies already underway. When required to be conducted, such studies must also be adequate and well-controlled. The applicant shall carry out any such studies with due diligence.

§314.520 Approval with restrictions to assure safe use.

(a) If FDA concludes that a drug product shown to be effective can be safely used only if distribution or use is restricted, FDA will require such postmarketing restrictions as are needed to assure safe use of the drug product, such as:

(1) Distribution restricted to certain facilities or physicians with special training or experience; or

(2) Distribution conditioned on the performance of specified medical procedures.

(b) The limitations imposed will be commensurate with the specific safety concerns presented by the drug product.

§314.530 Withdrawal procedures.

(a) For new drugs approved under §§314.510 and 314.520, FDA may withdraw approval, following a hearing as provided in part 15 of this chapter, as modified by this section, if:

(1) A postmarketing clinical study fails to verify clinical benefit;

(2) The applicant fails to perform the required postmarketing study with due diligence;

(3) Use after marketing demonstrates that postmarketing restrictions are inadequate to assure safe use of the drug product;

(4) The applicant fails to adhere to the postmarketing restrictions agreed upon;

(5) The promotional materials are false or misleading; or

(6) Other evidence demonstrates that the drug product is not shown to be safe or effective under its conditions of use.

(b) Notice of opportunity for a hearing. The Director of the Center for Drug Evaluation and Research will give the applicant notice of an opportunity for a hearing on the Center's proposal to withdraw the approval of an application approved under §314.510 or 314.520. The notice, which will ordinarily be a letter, will state generally the reasons for the action and the proposed grounds for the order.

(c) Submission of data and information.

(1) If the applicant fails to file a written request for a hearing within 15 days of receipt of the notice, the applicant waives the opportunity for a hearing.
(2) If the applicant files a timely request for a hearing, the agency will publish a notice of hearing in the Federal Register in accordance with §§12.32(e) and 15.20 of this chapter.

(3) An applicant who requests a hearing under this section must, within 30 days of receipt of the notice of opportunity for a hearing, submit the data and information upon which the applicant intends to rely at the hearing.

(d) Separation of functions. Separation of functions (as specified in §10.55 of this chapter) will not apply at any point in withdrawal proceedings under this section.

(e) Procedures for hearings. Hearings held under this section will be conducted in accordance with the provisions of part 15 of this chapter, with the following modifications:

(1) An advisory committee duly constituted under part 14 of this chapter will be present at the hearing. The committee will be asked to review the issues involved and to provide advice and recommendations to the Commissioner of Food and Drugs.

(2) The presiding officer, the advisory committee members, up to three representatives of the applicant, and up to three representatives of the Center may question any person during or at the conclusion of the person's presentation. No other person attending the hearing may question a person making a presentation. The presiding officer may, as a matter of discretion, permit questions to be submitted to the presiding officer for response by a person making a presentation.

(f) Judicial review. The Commissioner's decision constitutes final agency action from which the applicant may petition for judicial review. Before requesting an order from a court for a stay of action pending review, an applicant must first submit a petition for a stay of action under §10.35 of this chapter.

[57 FR 58958, Dec. 11, 1992, as amended at 64 FR 402, Jan. 5, 1999]

§314.540 Postmarketing safety reporting.

Drug products approved under this program are subject to the postmarketing recordkeeping and safety reporting applicable to all approved drug products, as provided in §§314.80 and 314.81.

§314.550 Promotional materials.

For drug products being considered for approval under this subpart, unless otherwise informed by the agency, applicants must submit to the agency for consideration during the preapproval review period copies of all promotional materials, including promotional labeling as well as advertisements, intended for dissemination or publication within 120 days following marketing approval. After 120 days following marketing approval, unless otherwise informed by the agency, the applicant must submit promotional materials at least 30 days prior to the intended time of initial dissemination of the labeling or initial publication of the advertisement.
§314.560 Termination of requirements.

If FDA determines after approval that the requirements established in §314.520, §314.530, or §314.550 are no longer necessary for the safe and effective use of a drug product, it will so notify the applicant. Ordinarily, for drug products approved under §314.510, these requirements will no longer apply when FDA determines that the required postmarketing study verifies and describes the drug product's clinical benefit and the drug product would be appropriate for approval under traditional procedures. For drug products approved under §314.520, the restrictions would no longer apply when FDA determines that safe use of the drug product can be assured through appropriate labeling. FDA also retains the discretion to remove specific postapproval requirements upon review of a petition submitted by the sponsor in accordance with §10.30.
§361.1 Radioactive drugs for certain research uses.

(a) Radioactive drugs (as defined in §310.3(n) of this chapter) are generally recognized as safe and effective when administered, under the conditions set forth in paragraph (b) of this section, to human research subjects during the course of a research project intended to obtain basic information regarding the metabolism (including kinetics, distribution, and localization) of a radioactively labeled drug or regarding human physiology, pathophysiology, or biochemistry, but not intended for immediate therapeutic, diagnostic, or similar purposes or to determine the safety and effectiveness of the drug in humans for such purposes (i.e., to carry out a clinical trial). Certain basic research studies, e.g., studies to determine whether a drug localizes in a particular organ or fluid space and to describe the kinetics of that localization, may have eventual therapeutic or diagnostic implications, but the initial studies are considered to be basic research within the meaning of this section.

(b) The conditions under which use of radioactive drugs for research are considered safe and effective are:

(1) Approval by Radioactive Drug Research Committee. A Radioactive Drug Research Committee, composed and approved by the Food and Drug Administration in accordance with paragraph (c) of this section, has determined, in accordance with the standards set forth in paragraph (d) of this section, that:
   (i) The pharmacological dose is within the limits set forth in paragraph (b)(2) of this section;
   (ii) The radiation dose is within the limits set forth in paragraph (b)(3) of this section;
   (iii) The radiation exposure is justified by the quality of the study being undertaken and the importance of the information it seeks to obtain;
   (iv) The study meets the other requirements set forth in paragraph (d) of this section regarding qualifications of the investigator, proper licensure for handling radioactive materials, selection and consent of research subjects, quality of radioactive drugs used, research protocol design, reporting of adverse reactions, and approval by an appropriate Institutional Review Committee; and
   (v) The use of the radioactive drug in human subjects has the approval of the Radioactive Drug Research Committee.

(2) Limit on pharmacological dose. The amount of active ingredient or combination of active ingredients to be administered shall be known not to cause any clinically detectable pharmacological effect in human beings. If the same active ingredients (exclusive of the radionuclide) are to be administered simultaneously, e.g., under a “Investigational New Drug Application” or for a
therapeutic use in accordance with labeling for a drug approved under part 314 of this chapter, the total amount of active ingredients including the radionuclide shall be known not to exceed the dose limitations applicable to the separate administration of the active ingredients excluding the radionuclide.

(3) Limit on radiation dose. The amount of radioactive material to be administered shall be such that the subject receives the smallest radiation dose with which it is practical to perform the study without jeopardizing the benefits to be obtained from the study.

(i) Under no circumstances may the radiation dose to an adult research subject from a single study or cumulatively from a number of studies conducted within 1 year be generally recognized as safe if such dose exceeds the following: Whole body, active blood-forming organs, lens of the eye, and gonads:

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<th>Rems</th>
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<tr>
<td>Single dose</td>
<td>3</td>
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<tr>
<td>Annual and total dose commitment</td>
<td>5</td>
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<tr>
<td>Other organs: Single dose</td>
<td>5</td>
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<tr>
<td>Annual and total dose commitment</td>
<td>15</td>
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(ii) For a research subject under 18 years of age at his last birthday, the radiation dose shall not exceed 10 percent of that set forth in paragraph (b)(3)(i) of this section.

(iii) All radioactive material included in the drug either as essential material or as a significant contaminant or impurity shall be included when determining the total radiation doses and dose commitments. Radiation doses from x-ray procedures that are part of the research study (i.e., would not have occurred but for the study) shall also be included. The possibility of followup studies shall be considered for inclusion in the dose calculations.

(iv) Numerical definitions of dose shall be based on an absorbed fraction method of radiation absorbed dose calculation, such as the system set forth by the Medical Internal Radiation Dose Committee of the Society of Nuclear Medicine, or the system set forth by the International Commission on Radiological Protection.

(c) A Radioactive Drug Research Committee, in order to comply with paragraph (b)(1) of this section, shall be composed, shall function, and shall obtain and maintain approval of the Food and Drug Administration in conformity with the following:

(1) Membership. A Radioactive Drug Research Committee shall consist of at least five individuals. Each committee shall include the following three individuals:

(i) A physician recognized as a specialist in nuclear medicine,

(ii) a person qualified by training and experience to formulate radioactive drugs, and

(iii) a person with special competence in radiation safety and radiation dosimetry. The remainder of the committee shall consist of individuals qualified in various disciplines pertinent to the field of nuclear medicine (e.g., radiology, internal medicine, clinical pathology, hematology, endocrinology, radiation therapy, radiation physics, radiation biophysics,
health physics, and radiopharmacy). Membership shall be sufficiently diverse to permit expert review of the technical and scientific aspects of proposals submitted to the committee. The addition of consultants in other pertinent medical disciplines is encouraged. A Radioactive Drug Research Committee shall be either associated with a medical institution operated for care of patients and with sufficient scientific expertise to allow for selection of committee members from its faculty, or with a committee established by a State authority to provide advice on radiation health matters. Joint committees involving more than one medical institution which have been established in order to achieve a high level and diversity of experience will be acceptable. The Director of the Center for Drug Evaluation and Research may modify any of the foregoing requirements in a particular situation where alternative factors provide substantially the same composition and association.

(2) Function. Each Radioactive Drug Research Committee shall select a chairman, who shall sign all applications, minutes, and reports of the committee. Each committee shall meet at least once each quarter in which research activity has been authorized or conducted. A quorum consisting of more than 50 percent of the membership must be present with appropriate representation of the required fields of specialization. Minutes shall be kept and shall include the numerical results of votes on protocols involving use in human subjects. No member shall vote on a protocol in which he is an investigator.

(3) Reports. Each Radioactive Drug Research Committee shall submit an annual report on or before January 31 of each year to the Food and Drug Administration, Center for Drug Evaluation and Research, HFD-160, 5600 Fishers Lane, Rockville, MD 20857. The annual report shall include the names and qualifications of the members of, and of any consultants used by, the Radioactive Drug Research Committee, and, for each study conducted during the preceding year, a summary of information presented in the following format:

Report on Research Use of Radioactive Drug

1. Title of the research project.
2. Brief description of the purpose of the research project.
3. Name of the investigator responsible.
5. Name of the radionuclide(s) used, including any present, as significant contaminants or impurities.
6. Radiation absorbed dose. Provide the maximum dose commitment to the whole body and each organ specified in 21 CFR 361.1(b)(3)(i) that was received by a representative subject and the calculations or references that were used to estimate these maximum dose commitments. The report shall include the dose contribution of both the administered radionuclide(s) and any X-ray procedures associated with the study. If the study elicits data on the uptake or excretion of
the radioactive drug pertinent to the estimation of dose commitment, report the mean value and range of values. For each subject provide:

(a) Age, sex, and approximate weight.

(b) Total activity of each radionuclide administered for each radioactive drug used in the study. Report each X-ray procedure used in conjunction with the study.

(c) If the subject has participated in other radioactive drug research studies, report the name of the radioactive drug used in these other studies, the date of administration, and the total activity of each radionuclide administered. If any X-ray procedures were used, identify the X-ray procedure(s) and include an estimate of the absorbed radiation doses.

(d) If more than one administration of a radioactive drug per subject, cumulative radiation dose and dose commitment, expressed as whole body, active blood-forming organs, lens of the eye, gonads, and other organ doses from the administered radionuclides. 7. A claim of confidentiality, if any. Note: Contents of this report are available for public disclosure unless confidentiality is requested by the investigator and it is adequately shown by the investigator that the report constitutes a trade secret or confidential commercial information as defined in 21 CFR 20.61.

_________________________________________________
Investigator

________________________________________________
Chairman, Radioactive Drug Research Committee

At any time a proposal is approved which involves exposure either of more than 30 research subjects, or of any research subject under 18 years of age, the committee shall immediately submit to the Food and Drug Administration a special summary of information in the format shown in this paragraph. Contents of these reports are available for public disclosure, unless confidentiality is requested by the investigator and it is adequately shown by the investigator that the report constitutes a trade secret or confidential commercial information as defined in §20.61 of this chapter.

(4) Approval. Each Radioactive Drug Research Committee shall be specifically approved by the Center for Drug Evaluation and Research of the Food and Drug Administration. Applications shall be submitted to the Food and Drug Administration, Center for Drug Evaluation and Research, HFD-160, 5600 Fishers Lane, Rockville, MD 20857, and shall contain the names and qualifications of the members of the committee, and a statement that the committee agrees to comply with the requirements set forth in this section. Approval shall be based upon an assessment of the qualifications of the members of the committee, and the assurance that all necessary fields of expertise are covered. Approval of a committee may be withdrawn at any time for failure of the committee to comply with any of the requirements of this section. Approval of a committee shall remain effective unless and until the
FDA Human Research Regulations

FDA withdraws such approval. Changes in membership and applications for new members shall be submitted to the Food and Drug Administration as soon as, or before, vacancies occur on the committee.

(5) Monitoring. The Food and Drug Administration shall conduct periodic reviews of approved committees. Monitoring of the activities of the committee shall be conducted through review of its annual report, through review of minutes and full protocols for certain studies, and through on-site inspections.

(d) In making the determination required in paragraph (b)(1) of this section, a Radioactive Drug Research Committee shall consider the following requirements and assure that each is met:

(1) Radiation dose to subjects. To assure that the radiation dose to research subjects is as low as practicable to perform the study and meet the criteria of §361.1(b)(3), the Radioactive Drug Research Committee shall require that:

(i) The investigator provide absorbed dose calculations based on biologic distribution data available from published literature or from other valid studies.

(ii) The investigator provide for an acceptable method of radioassay of the radioactive drug prior to its use to assure that the dose calculations actually reflect the administered dose.

(iii) The radioactive drug chosen for the study has that combination of half-life, types of radiations, radiation energy, metabolism, chemical properties, etc., which results in the lowest dose to the whole body or specific organs with which it is possible to obtain the necessary information.

(iv) The investigator utilize adequate and appropriate instrumentation for the detection and measurement of the specific radionuclide.

(2) Pharmacological dosage. To determine that the amount of active ingredients to be administered does not exceed the limitations set forth in paragraph (b)(2) of this section, the committee shall require that the investigator provide pharmacological dose calculations based on data available from published literature or from other valid human studies.

(3) Qualifications of investigators. Each investigator shall be qualified by training and experience to conduct the proposed research studies.

(4) License to handle radioactive materials. The responsible investigator or institutions shall, in the case of reactor-produced isotopes, be licensed by the Nuclear Regulatory Commission or Agreement State to possess and use the specific radionuclides for research use or be a listed investigator under a broad license, or in the case of non-reactor-produced isotopes, be licensed by other appropriate State or local authorities, when required by State or local law, to possess and use the specific radionuclides for research use.

(5) Human research subjects. Each investigator shall select appropriate human subjects and shall obtain the review and approval of an institutional review committee that conforms to the requirements of part 56 of this chapter, and shall obtain the consent of the subjects or their legal representatives in accordance with part 50 of this chapter. The research subjects shall be at least 18 years of age and legally competent. Exceptions are permitted only in those special situations when it can be demonstrated to the committee that the study presents
a unique opportunity to gain information not currently available, requires the use of research subjects less than 18 years of age, and is without significant risk to the subject. Studies involving minors shall be supported with review by qualified pediatric consultants to the Radioactive Drug Research Committee. Each female research subject of childbearing potential shall state in writing that she is not pregnant, or, on the basis of a pregnancy test be confirmed as not pregnant, before she may participate in any study.

(6) Quality of radioactive drug. The radioactive drug used in the research study shall meet appropriate chemical, pharmaceutical, radiochemical, and radionuclidic standards of identity, strength, quality, and purity as needed for safety and be of such uniform and reproducible quality as to give significance to the research study conducted. The Radioactive Drug Research Committee shall determine that radioactive materials for parenteral use are prepared in sterile and pyrogen-free form.

(7) Research protocol. No matter how small the amount of radioactivity, no study involving administration of a radioactive drug, as defined in §310.3(n) of this chapter, to research subjects under this section, shall be permitted unless the Radioactive Drug Research Committee concludes, in its judgment, that scientific knowledge and benefit is likely to result from that study. Therefore, the protocol shall be based upon a sound rationale derived from appropriate animal studies or published literature and shall be of sound design such that information of scientific value may result. The radiation dose shall be both sufficient and no greater than necessary to obtain valid measurement. The projected number of subjects shall be sufficient but no greater than necessary for the purpose of the study. The number of subjects shall also reflect the fact that the study is intended to obtain basic research information referred to in paragraph (a) of this section and not intended for immediate therapeutic, diagnostic or similar purposes or to determine the safety and effectiveness of the drug in humans for such purposes (i.e., to carry out a clinical trial).

(8) Adverse reactions. The investigator shall immediately report to the Radioactive Drug Research Committee all adverse effects associated with the use of the radioactive drug in the research study. All adverse reactions probably attributable to the use of the radioactive drug in the research study shall be immediately reported by the Radioactive Drug Research Committee to the Food and Drug Administration, Center for Drug Evaluation and Research, HFD-160, 5600 Fishers Lane, Rockville, MD 20857.

(9) Approval by an institutional review board. The investigator shall obtain the review and approval of an institutional review board that conforms to the requirements of part 56 of this chapter.

(e) The results of any research conducted pursuant to this section as part of the evaluation of a drug pursuant to part 312 of this chapter shall be included in the submissions required under part 312 of this chapter.

(f) A radioactive drug prepared, packaged, distributed, and primarily intended for use in accordance with the requirements of this section shall be exempt from section 502(f)(1) of the act and Secs. 201.5 and 201.100 of this chapter if the packaging, label, and labeling are in compliance with Federal, State, and local law regarding
radioactive materials and if the label of the immediate container and shielded
container, if any, either separate from or as part of any label and labeling required for
radioactive materials by the Nuclear Regulatory Commission or by State or local
radiological health authorities bear the following:
(1) The statement “Caution: Federal law prohibits dispensing without prescription”;
(2) The statement “To be administered in compliance with the requirements of
Federal regulations regarding radioactive drugs for research use (21 CFR
361.1)”;
(3) The established name of the drug, if any;
(4) The established name and quantity of each active ingredient;
(5) The name and half-life of the radionuclide, total quantity of radioactivity in the
drug product's immediate container, and amount of radioactivity per unit
volume or unit mass at a designated referenced time;
(6) The route of administration, if it is for the other than oral use;
(7) The net quantity of contents;
(8) An identifying lot or control number from which it is possible to determine the
complete manufacturing history of the package of the drug;
(9) The name and address of the manufacturer, packer, or distributor;
(10) The expiration date, if any;
(11) If the drug is intended for parenteral use, a statement as to whether the contents
are sterile;
(12) If the drug is for other than oral use, the names of all inactive ingredients, except
that:
   (i) Trace amounts of harmless substances added solely for individual product
identification need not be named.
   (ii) If the drug is intended for parenteral use, the quantity or proportion of all
inactive ingredients, except that ingredients added to adjust pH or to make
the drug isotonic may be declared by name and a statement of their effect;
if the vehicle is water for injection, it need not be named. Provided,
however, That in the case of containers too small or otherwise unable to
accommodate a label with sufficient space to bear all such information, the
information required by paragraphs (f)(1) and (12) of this section may be
placed on the shielded container only.

[40 FR 31308, July 25, 1975, as amended at 40 FR 44543, Sept. 29, 1975; 42 FR 15674, Mar. 22, 1977; 43
FR 14646, Apr. 7, 1978; 46 FR 8955, Jan. 27, 1981; 49 FR 44460, Nov. 7, 1984; 50 FR 8996, Mar. 6,
21 CFR 600--BIOLOGICAL PRODUCTS: GENERAL

Subpart A--General Provisions

§600.3 Definitions.
As used in this subchapter:
(a) Act means the Public Health Service Act (58 Stat. 682), approved July 1, 1944.
(b) Secretary means the Secretary of Health and Human Services and any other officer or employee of the Department of Health and Human Services to whom the authority involved has been delegated.
(c) Commissioner of Food and Drugs means the Commissioner of the Food and Drug Administration.
(d) Center for Biologics Evaluation and Research means Center for Biologics Evaluation and Research of the Food and Drug Administration.
(e) State means a State or the District of Columbia, Puerto Rico, or the Virgin Islands.
(f) Possession includes among other possessions, Puerto Rico and the Virgin Islands.
(g) Products includes biological products and trivalent organic arsenicals.
(h) Biological product means any virus, therapeutic serum, toxin, antitoxin, or analogous product applicable to the prevention, treatment or cure of diseases or injuries of man:
   (1) A virus is interpreted to be a product containing the minute living cause of an infectious disease and includes but is not limited to filterable viruses, bacteria, rickettsia, fungi, and protozoa.
   (2) A therapeutic serum is a product obtained from blood by removing the clot or clot components and the blood cells.
   (3) A toxin is a product containing a soluble substance poisonous to laboratory animals or to man in doses of 1 milliliter or less (or equivalent in weight) of the product, and having the property, following the injection of non-fatal doses into an animal, of causing to be produced therein another soluble substance which specifically neutralizes the poisonous substance and which is demonstrable in the serum of the animal thus immunized.
   (4) An antitoxin is a product containing the soluble substance in serum or other body fluid of an immunized animal which specifically neutralizes the toxin against which the animal is immune.
   (5) A product is analogous:
      (i) To a virus if prepared from or with a virus or agent actually or potentially infectious, without regard to the degree of virulence or toxicogenicity of the specific strain used.
      (ii) To a therapeutic serum, if composed of whole blood or plasma or containing some organic constituent or product other than a hormone or an amino acid, derived from whole blood, plasma, or serum.
      (iii) To a toxin or antitoxin, if intended, irrespective of its source of origin, to be applicable to the prevention, treatment, or cure of disease or injuries of man through a specific immune process.
(i) **Trivalent organic arsenicals** means arsphenamine and its derivatives (or any other trivalent organic arsenic compound) applicable to the prevention, treatment, or cure of diseases or injuries of man.

(j) A product is deemed applicable to the prevention, treatment, or cure of diseases or injuries of man irrespective of the mode of administration or application recommended, including use when intended through administration or application to a person as an aid in diagnosis, or in evaluating the degree of susceptibility or immunity possessed by a person, and including also any other use for purposes of diagnosis if the diagnostic substance so used is prepared from or with the aid of a biological product.

(k) **Proper name**, as applied to a product, means the name designated in the license for use upon each package of the product.

(l) **Dating period** means the period beyond which the product cannot be expected beyond reasonable doubt to yield its specific results.

(m) **Expiration date** means the calendar month and year, and where applicable, the day and hour, that the dating period ends.

(n) The word **standards** means specifications and procedures applicable to an establishment or to the manufacture or release of products, which are prescribed in this subchapter or established in the biologics license application designed to insure the continued safety, purity, and potency of such products.

(o) The word **continued** as applied to the safety, purity and potency of products is interpreted to apply to the dating period.

(p) The word **safety** means the relative freedom from harmful effect to persons affected, directly or indirectly, by a product when prudently administered, taking into consideration the character of the product in relation to the condition of the recipient at the time.

(q) The word **sterility** is interpreted to mean freedom from viable contaminating microorganisms, as determined by the tests prescribed in §610.12 of this chapter.

(r) **Purity** means relative freedom from extraneous matter in the finished product, whether or not harmful to the recipient or deleterious to the product. Purity includes but is not limited to relative freedom from residual moisture or other volatile substances and pyrogenic substances.

(s) The word **potency** is interpreted to mean the specific ability or capacity of the product, as indicated by appropriate laboratory tests or by adequately controlled clinical data obtained through the administration of the product in the manner intended, to effect a given result.

(t) **Manufacturer** means any legal person or entity engaged in the manufacture of a product subject to license under the act; “Manufacturer” also includes any legal person or entity who is an applicant for a license where the applicant assumes responsibility for compliance with the applicable product and establishment standards.

(u) **Manufacture** means all steps in propagation or manufacture and preparation of products and includes but is not limited to filling, testing, labeling, packaging, and storage by the manufacturer.
(v) **Location** includes all buildings, appurtenances, equipment and animals used, and personnel engaged by a manufacturer within a particular area designated by an address adequate for identification.

(w) **Establishment** has the same meaning as “facility” in section 351 of the Public Health Service Act and includes all locations.

(x) **Lot** means that quantity of uniform material identified by the manufacturer as having been thoroughly mixed in a single vessel.

(y) A filling refers to a group of final containers identical in all respects, which have been filled with the same product from the same bulk lot without any change that will affect the integrity of the filling assembly.

(z) **Process** refers to a manufacturing step that is performed on the product itself which may affect its safety, purity or potency, in contrast to such manufacturing steps which do not affect intrinsically the safety, purity or potency of the product.

(aa) **Selling agent or distributor** means any person engaged in the unrestricted distribution, other than by sale at retail, of products subject to license.

(bb) **Container** (referred to also as “final container”) is the immediate unit, bottle, vial, ampule, tube, or other receptacle containing the product as distributed for sale, barter, or exchange.

(cc) **Package** means the immediate carton, receptacle, or wrapper, including all labeling matter therein and thereon, and the contents of the one or more enclosed containers. If no package, as defined in the preceding sentence, is used, the container shall be deemed to be the package.

(dd) **Label** means any written, printed, or graphic matter on the container or package or any such matter clearly visible through the immediate carton, receptacle, or wrapper.

(ee) **Radioactive biological product** means a biological product which is labeled with a radionuclide or intended solely to be labeled with a radionuclide.

(ff) **Amendment** is the submission of information to a pending license application or supplement, to revise or modify the application as originally submitted.

(gg) **Supplement** is a request to the Director, Center for Biologics Evaluation and Research, to approve a change in an approved license application.

(hh) **Distributed** means the biological product has left the control of the licensed manufacturer.

(ii) **Control** means having responsibility for maintaining the continued safety, purity, and potency of the product and for compliance with applicable product and establishment standards, and for compliance with current good manufacturing practices.

**Subpart B--Establishment Standards**

§600.10 **Personnel.**

(a) [Reserved]

(b) Personnel. Personnel shall have capabilities commensurate with their assigned functions, a thorough understanding of the manufacturing operations which they perform, the necessary training and experience relating to individual products, and adequate information concerning the application of the pertinent provisions of this subchapter to their respective functions. Personnel shall include such professionally
trained persons as are necessary to insure the competent performance of all manufacturing processes.

(c) Restrictions on personnel--(1) Specific duties. Persons whose presence can affect adversely the safety and purity of a product shall be excluded from the room where the manufacture of a product is in progress.

(2) Sterile operations. Personnel performing sterile operations shall wear clean or sterilized protective clothing and devices to the extent necessary to protect the product from contamination.

(3) Pathogenic viruses and spore-bearing organisms. Persons working with viruses pathogenic for man or with spore-bearing microorganisms, and persons engaged in the care of animals or animal quarters, shall be excluded from areas where other products are manufactured, or such persons shall change outer clothing, including shoes, or wear protective covering prior to entering such areas.

(4) Live vaccine work areas. Persons may not enter a live vaccine processing area after having worked with other infectious agents in any other laboratory during the same working day. Only persons actually concerned with propagation of the culture, production of the vaccine, and unit maintenance, shall be allowed in live vaccine processing areas when active work is in progress. Casual visitors shall be excluded from such units at all times and all others having business in such areas shall be admitted only under supervision. Street clothing, including shoes, shall be replaced or covered by suitable laboratory clothing before entering a live vaccine processing unit. Persons caring for animals used in the manufacture of live vaccines shall be excluded from other animal quarters and from contact with other animals during the same working day.

§600.11 Physical establishment, equipment, animals, and care.

(a) Work areas. All rooms and work areas where products are manufactured or stored shall be kept orderly, clean, and free of dirt, dust, vermin and objects not required for manufacturing. Precautions shall be taken to avoid clogging and back-siphonage of drainage systems. Precautions shall be taken to exclude extraneous infectious agents from manufacturing areas. Work rooms shall be well lighted and ventilated. The ventilation system shall be arranged so as to prevent the dissemination of microorganisms from one manufacturing area to another and to avoid other conditions unfavorable to the safety of the product. Filling rooms, and other rooms where open, sterile operations are conducted, shall be adequate to meet manufacturing needs and such rooms shall be constructed and equipped to permit thorough cleaning and to keep air-borne contaminants at a minimum. If such rooms are used for other purposes, they shall be cleaned and prepared prior to use for sterile operations. Refrigerators, incubators and warm rooms shall be maintained at temperatures within applicable ranges and shall be free of extraneous material which might affect the safety of the product.

(b) Equipment. Apparatus for sterilizing equipment and the method of operation shall be such as to insure the destruction of contaminating microorganisms. The effectiveness of the sterilization procedure shall be no less than that achieved by an attained temperature of 121.5 deg. C maintained for 20 minutes by saturated steam or by an attained temperature of 170 deg. C maintained for 2 hours with dry heat. Processing
and storage containers, filters, filling apparatus, and other pieces of apparatus and accessory equipment, including pipes and tubing, shall be designed and constructed to permit thorough cleaning and, where possible, inspection for cleanliness. All surfaces that come in contact with products shall be clean and free of surface solids, leachable contaminants, and other materials that will hasten the deterioration of the product or otherwise render it less suitable for the intended use. For products for which sterility is a factor, equipment shall be sterile, unless sterility of the product is assured by subsequent procedures.

c) Laboratory and bleeding rooms. Rooms used for the processing of products, including bleeding rooms, shall be effectively fly-proofed and kept free of flies and vermin. Such rooms shall be so constructed as to insure freedom from dust, smoke and other deleterious substances and to permit thorough cleaning and disinfection. Rooms for animal injection and bleeding, and rooms for smallpox vaccine animals, shall be disinfected and be provided with the necessary water, electrical and other services.

d) Animal quarters and stables. Animal quarters, stables and food storage areas shall be of appropriate construction, fly-proofed, adequately lighted and ventilated, and maintained in a clean, vermin-free and sanitary condition. No manure or refuse shall be stored as to permit the breeding of flies on the premises, nor shall the establishment be located in close proximity to off-property manure or refuse storage capable of engendering fly breeding.

(e) Restrictions on building and equipment use—

1) Work of a diagnostic nature. Laboratory procedures of a clinical diagnostic nature involving materials that may be contaminated, shall not be performed in space used for the manufacture of products except that manufacturing space which is used only occasionally may be used for diagnostic work provided spore-bearing pathogenic microorganisms are not involved and provided the space is thoroughly cleaned and disinfected before the manufacture of products is resumed.

2) Spore-bearing organisms for supplemental sterilization procedure control test. Spore-bearing organisms used as an additional control in sterilization procedures may be introduced into areas used for the manufacture of products, only for the purposes of the test and only immediately before use for such purposes: Provided, That (i) the organism is not pathogenic for man or animals and does not produce pyrogens or toxins, (ii) the culture is demonstrated to be pure, (iii) transfer of test cultures to culture media shall be limited to the sterility test area or areas designated for work with spore-bearing organisms, (iv) each culture be labeled with the name of the microorganism and the statement “Caution: microbial spores. See directions for storage, use and disposition.”, and (v) the container of each culture is designed to withstand handling without breaking.

3) Work with spore-bearing organisms. Except as provided in the previous paragraph, all work with spore-bearing microorganisms shall be done in an entirely separate building: Provided, That such work may be done in a portion...
of a building used in the manufacture of products not containing spore-bearing microorganisms if such portion is completely walled-off and is constructed so as to prevent contamination of other areas and if entrances to such portion are independent of the remainder of the building. All vessels, apparatus and equipment used for spore-bearing microorganisms shall be permanently identified and reserved exclusively for use with those organisms. Materials destined for further manufacturing may be removed from such an area only under conditions which will prevent the introduction of spores into other manufacturing areas.

(4) Live vaccine processing. Space used for processing a live vaccine shall not be used for any other purpose during the processing period for that vaccine and such space shall be decontaminated prior to initiation of the processing. Live vaccine processing areas shall be isolated from and independent of any space used for any other purpose by being either in a separate building, in a separate wing of a building, or in quarters at the blind end of a corridor and shall include adequate space and equipment for all processing steps up to filling into final containers. Test procedures which potentially involve the presence of microorganisms other than the vaccine strains, or the use of tissue culture cell lines other than primary cultures, shall not be conducted in space used for processing live vaccine.

(5) Equipment and supplies--contamination. Equipment and supplies used in work on or otherwise exposed to any pathogenic or potentially pathogenic agent shall be kept separated from equipment and supplies used in the manufacture of products to the extent necessary to prevent cross-contamination.

(f) Animals used in manufacture—

(1) Care of animals used in manufacturing. Caretakers and attendants for animals used for the manufacture of products shall be sufficient in number and have adequate experience to insure adequate care. Animal quarters and cages shall be kept in sanitary condition. Animals on production shall be inspected daily to observe response to production procedures. Animals that become ill for reasons not related to production shall be isolated from other animals and shall not be used for production until recovery is complete. Competent veterinary care shall be provided as needed.

(2) Quarantine of animals—

(i) General. No animal shall be used in processing unless kept under competent daily inspection and preliminary quarantine for a period of at least 7 days before use, or as otherwise provided in this subchapter. Only healthy animals free from detectable communicable diseases shall be used. Animals must remain in overt good health throughout the quarantine periods and particular care shall be taken during the quarantine periods to reject animals of the equine genus which may be infected with glanders and animals which may be infected with tuberculosis.

(ii) Quarantine of monkeys. In addition to observing the pertinent general quarantine requirements, monkeys used as a source of tissue in the manufacture of vaccine shall be maintained in quarantine for at least 6 weeks prior to use, except when otherwise provided in this part. Only
particles that have reacted negatively to tuberculin at the start of the
quarantine period and again within 2 weeks prior to use shall be used in
the manufacture of vaccine. Due precaution shall be taken to prevent
cross-infection from any infected or potentially infected monkeys on the
premises. Monkeys to be used in the manufacture of a live vaccine shall be
maintained throughout the quarantine period in cages closed on all sides
with solid materials except the front which shall be screened, with no
more than two monkeys housed in one cage. Cage mates shall not be
interchanged.

(3) Immunization against tetanus. Horses and other animals susceptible to tetanus,
that are used in the processing steps of the manufacture of biological products,
shall be treated adequately to maintain immunity to tetanus.

(4) Immunization and bleeding of animals used as a source of products. Toxins or
other nonviable antigens administered in the immunization of animals used in
the manufacture of products shall be sterile. Viable antigens, when so used,
shall be free of contaminants, as determined by appropriate tests prior to use.
Injections shall not be made into horses within 6 inches of bleeding site. Horses
shall not be bled for manufacturing purposes while showing persistent general
reaction or local reaction near the site of bleeding. Blood shall not be used if it
was drawn within 5 days of injecting the animals with viable microorganisms.
Animals shall not be bled for manufacturing purposes when they have an
intercurrent disease. Blood intended for use as a source of a biological product
shall be collected in clean, sterile vessels. When the product is intended for use
by injection, such vessels shall also be pyrogen-free.

(5) [Reserved]

(6) Reporting of certain diseases. In cases of actual or suspected infection with foot
and mouth disease, glanders, tetanus, anthrax, gas gangrene, equine infectious
anemia; equine encephalomyelitis, or any of the pock diseases among animals
intended for use or used in the manufacture of products, the manufacturer shall
immediately notify the Director, Center for Biologics Evaluation and Research.

(7) Monkeys used previously for experimental or test purposes. Monkeys that have
been used previously for experimental or test purposes with live microbiological
agents shall not be used as a source of kidney tissue for the manufacture of
vaccine. Except as provided otherwise in this subchapter, monkeys that have
been used previously for other experimental or test purposes may be used as a
source of kidney tissue upon their return to a normal condition, provided all
quarantine requirements have been met.

(8) Necropsy examination of monkeys. Each monkey used in the manufacture of
vaccine shall be examined at necropsy under the direction of a qualified
pathologist, physician, or veterinarian having experience with diseases of
monkeys, for evidence of ill health, particularly for
(i) evidence of tuberculosis,
(ii) presence of herpes-like lesions, including eruptions or plaques on or around
the lips, in the buccal cavity or on the gums, and
(iii) signs of conjunctivitis. If there are any such signs or other significant gross pathological lesions, the tissue shall not be used in the manufacture of vaccine.

(g) Filling procedures. Filling procedures shall be such as will not affect adversely the safety, purity or potency of the product.

(h) Containers and closures. All final containers and closures shall be made of material that will not hasten the deterioration of the product or otherwise render it less suitable for the intended use. All final containers and closures shall be clean and free of surface solids, leachable contaminants and other materials that will hasten the deterioration of the product or otherwise render it less suitable for the intended use. After filling, sealing shall be performed in a manner that will maintain the integrity of the product during the dating period. In addition, final containers and closures for products intended for use by injection shall be sterile and free from pyrogens. Except as otherwise provided in the regulations of this subchapter, final containers for products intended for use by injection shall be colorless and sufficiently transparent to permit visual examination of the contents under normal light. As soon as possible after filling final containers shall be labeled as prescribed in §610.60 et seq. of this chapter, except that final containers may be stored without such prescribed labeling provided they are stored in a sealed receptacle labeled both inside and outside with at least the name of the product, the lot number, and the filling identification.

§600.12 Records.

(a) Maintenance of records. Records shall be made, concurrently with the performance of each step in the manufacture and distribution of products, in such a manner that at any time successive steps in the manufacture and distribution of any lot may be traced by an inspector. Such records shall be legible and indelible, shall identify the person immediately responsible, shall include dates of the various steps, and be as detailed as necessary for clear understanding of each step by one experienced in the manufacture of products.

(b) Records retention—

(1) General. Records shall be retained for such interval beyond the expiration date as is necessary for the individual product, to permit the return of any clinical report of unfavorable reactions. The retention period shall be no less than five years after the records of manufacture have been completed or six months after the latest expiration date for the individual product, whichever represents a later date.

(2) Records of recall. Complete records shall be maintained pertaining to the recall from distribution of any product upon notification by the Director, Center for Biologics Evaluation and Research, to recall for failure to conform with the standards prescribed in the regulations of this subchapter, because of deterioration of the product or for any other factor by reason of which the distribution of the product would constitute a danger to health.

(3) Suspension of requirement for retention. The Director, Center for Biologics Evaluation and Research, may authorize the suspension of the requirement to retain records of a specific manufacturing step upon a showing that such records no longer
have significance for the purposes for which they were made: Provided, That a summary of such records shall be retained.
(c) Records of sterilization of equipment and supplies. Records relating to the mode of sterilization, date, duration, temperature and other conditions relating to each sterilization of equipment and supplies used in the processing of products shall be made by means of automatic recording devices or by means of a system of recording which gives equivalent assurance of the accuracy and reliability of the record. Such records shall be maintained in a manner that permits an identification of the product with the particular manufacturing process to which the sterilization relates.
(d) Animal necropsy records. A necropsy record shall be kept on each animal from which a biological product has been obtained and which dies or is sacrificed while being so used.
(e) Records in case of divided manufacturing responsibility. If two or more establishments participate in the manufacture of a product, the records of each such establishment must show plainly the degree of its responsibility. In addition, each participating manufacturer shall furnish to the manufacturer who prepares the product in final form for sale, barter or exchange, a copy of all records relating to the manufacturing operations performed by such participating manufacturer insofar as they concern the safety, purity and potency of the lots of the product involved, and the manufacturer who prepares the product in final form shall retain a complete record of all the manufacturing operations relating to the product.

§600.13 Retention samples.
Manufacturers shall retain for a period of at least 6 months after the expiration date, unless a different time period is specified in additional standards, a quantity of representative material of each lot of each product, sufficient for examination and testing for safety and potency, except Whole Blood, Cryoprecipitated AHF, Platelets, Red Blood Cells, Plasma, and Source Plasma and Allergenic Products prepared to a physician's prescription. Samples so retained shall be selected at random from either final container material, or from bulk and final containers, provided they include at least one final container as a final package, or package-equivalent of such filling of each lot of the product as intended for distribution. Such sample material shall be stored at temperatures and under conditions which will maintain the identity and integrity of the product. Samples retained as required in this section shall be in addition to samples of specific products required to be submitted to the Center for Biologics Evaluation and Research. Exceptions may be authorized by the Director, Center for Biologics Evaluation and Research, when the lot yields relatively few final containers and when such lots are prepared by the same method in large number and in close succession.

§600.14 Reporting of biological product deviations by licensed manufacturers.
(a) Who must report under this section?
   (1) You, the manufacturer who holds the biological product license and who had control over the product when the deviation occurred, must report under this section. If you arrange for another person to perform a manufacturing, holding, or distribution step, while the product is in your control, that step is performed
under your control. You must establish, maintain, and follow a procedure for receiving information from that person on all deviations, complaints, and adverse events concerning the affected product.

(2) Exceptions:

(i) Persons who manufacture only in vitro diagnostic products that are not subject to licensing under section 351 of the Public Health Service Act do not report biological product deviations for those products under this section but must report in accordance with part 803 of this chapter;

(ii) Persons who manufacture blood and blood components, including licensed manufacturers, unlicensed registered blood establishments, and transfusion services, do not report biological product deviations for those products under this section but must report under §606.171 of this chapter;

(iii) Persons who manufacture Source Plasma or any other blood component and use that Source Plasma or any other blood component in the further manufacture of another licensed biological product must report:

(A) Under §606.171 of this chapter, if a biological product deviation occurs during the manufacture of that Source Plasma or any other blood component; or

(B) Under this section, if a biological product deviation occurs after the manufacture of that Source Plasma or any other blood component, and during manufacture of the licensed biological product.

(b) What do I report under this section? You must report any event, and information relevant to the event, associated with the manufacturing, to include testing, processing, packing, labeling, or storage, or with the holding or distribution, of a licensed biological product, if that event meets all the following criteria:

(1) Either:

(i) Represents a deviation from current good manufacturing practice, applicable regulations, applicable standards, or established specifications that may affect the safety, purity, or potency of that product; or

(ii) Represents an unexpected or unforeseeable event that may affect the safety, purity, or potency of that product; and

(2) Occurs in your facility or another facility under contract with you; and

(3) Involves a distributed biological product.

(c) When do I report under this section? You should report a biological product deviation as soon as possible but you must report at a date not to exceed 45-calendar days from the date you, your agent, or another person who performs a manufacturing, holding, or distribution step under your control, acquire information reasonably suggesting that a reportable event has occurred.

(d) How do I report under this section? You must report on Form FDA-3486.

(e) Where do I report under this section? You must send the completed Form FDA-3486 to the Director, Office of Compliance and Biologics Quality (HFM-600), Center for Biologics Evaluation and Research, 1401 Rockville Pike, suite 200N, Rockville, MD 20852-1448, by either a paper or an electronic filing:

(1) If you make a paper filing, you should identify on the envelope that a BPDR (biological product deviation report) is enclosed; or
(2) If you make an electronic filing, you may submit the completed Form FDA-3486 electronically through CBER's website at http://www.fda.gov/cber.

(f) How does this regulation affect other FDA regulations? This part supplements and does not supersede other provisions of the regulations in this chapter. All biological product deviations, whether or not they are required to be reported under this section, should be investigated in accordance with the applicable provisions of parts 211 and 820 of this chapter.

§600.15 Temperatures during shipment.
The following products shall be maintained during shipment at the specified temperatures:

<table>
<thead>
<tr>
<th>Product</th>
<th>Temperature</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cryoprecipitated AHF</td>
<td>-18 °C or colder.</td>
</tr>
<tr>
<td>Measles and Rubella Virus Vaccine Live</td>
<td>10 °C or colder.</td>
</tr>
<tr>
<td>Measles Live and Smallpox Vaccine</td>
<td>Do.</td>
</tr>
<tr>
<td>Measles, Mumps, and Rubella Virus Vaccine Live</td>
<td>Do.</td>
</tr>
<tr>
<td>Measles and Mumps Virus Vaccine Live</td>
<td>Do.</td>
</tr>
<tr>
<td>Measles Virus Vaccine Live ..</td>
<td>Do.</td>
</tr>
<tr>
<td>Mumps Virus Vaccine Live ....</td>
<td>Do.</td>
</tr>
<tr>
<td>Fresh Frozen Plasma</td>
<td>-18 °C or colder.</td>
</tr>
<tr>
<td>Liquid Plasma</td>
<td>1 to 10 °C.</td>
</tr>
<tr>
<td>Plasma</td>
<td>-18 °C or colder.</td>
</tr>
<tr>
<td>Platelet Rich Plasma</td>
<td>Between 1 and 10 °C if the label indicates storage between 1 and 6 °C, or all reasonable methods to maintain the temperature storage between 20 and 24 °C. as close as possible to a range between 20 and 24°C, if the label indicates.</td>
</tr>
<tr>
<td>Platelets</td>
<td>Between 1 and 10 °C if the label indicates storage between 1 and 6 °C, or all reasonable methods to maintain the temperature as close as possible to a range between 20 to 24 °C, if the label indicates.</td>
</tr>
<tr>
<td>Poliovirus Vaccine Live Oral Trivalent</td>
<td>0 °C or colder.</td>
</tr>
<tr>
<td>Poliovirus Vaccine Live Oral Type I.</td>
<td>Do.</td>
</tr>
<tr>
<td>Poliovirus Vaccine Live Oral Type II.</td>
<td>Do.</td>
</tr>
<tr>
<td>Poliovirus Vaccine Live Oral Type III.</td>
<td>Do.</td>
</tr>
<tr>
<td>Red Blood Cells (liquid product).</td>
<td>Between 1 and 10 °C.</td>
</tr>
</tbody>
</table>
Red Blood Cells Frozen ........ -65 °C or colder.
Rubella and Mumps Virus Vaccine Live. 10 °C or colder.
Rubella Virus Vaccine Live ... Do
Smallpox Vaccine (Liquid Product). 0 °C or colder.
Source Plasma ..................... -5 °C or colder.
Source Plasma Liquid ........... 10 °C or colder.
Whole Blood ........................ Blood that is transported from the collecting facility to the processing facility shall be transported in an environment capable of continuously cooling the blood toward a temperature range of 1 to 10 °C, or at a temperature as close as possible to 20 to 24 °C for a period not to exceed 6 hours. Blood transported from the storage facility shall be placed in an appropriate environment to maintain a temperature range between 1 to 10 °C during shipment.
Yellow Fever Vaccine .......... 0 °C or colder.

(b) Exemptions. Exemptions or modifications shall be made only upon written approval, in the form of a supplement to the biologics license application, approved by the Director, Center for Biologics Evaluation and Research.

Subpart C--Establishment Inspection

§600.20 Inspectors.
Inspections shall be made by an officer of the Food and Drug Administration having special knowledge of the methods used in the manufacture and control of products and designated for such purposes by the Commissioner of Food and Drugs, or by any officer, agent, or employee of the Department of Health and Human Services specifically designated for such purpose by the Secretary.

§600.21 Time of inspection.
The inspection of an establishment for which a biologics license application is pending need not be made until the establishment is in operation and is manufacturing the complete product for which a biologics license is desired. In case the license is denied following inspection for the original license, no reinspection need be made until assurance has been received that the faulty conditions which were the basis of the denial have been corrected. An inspection of each licensed establishment and its additional location(s) shall be made at least once every 2 years. Inspections may be made with or
without notice, and shall be made during regular business hours unless otherwise directed.

§600.22 Duties of inspector.
The inspector shall:
(a) Call upon the active head of the establishment, stating the object of his visit,
(b) Interrogate the proprietor or other personnel of the establishment as he may deem necessary,
(c) Examine the details of location, construction, equipment and maintenance, including stables, barns, warehouses, manufacturing laboratories, bleeding clinics maintained for the collection of human blood, shipping rooms, record rooms, and any other structure or appliance used in any part of the manufacture of a product,
(d) Investigate as fully as he deems necessary the methods of propagation, processing, testing, storing, dispensing, recording, or other details of manufacture and distribution of each licensed product, or product for which a license has been requested, including observation of these procedures in actual operation,
(e) Obtain and cause to be sent to the Director, Center for Biologics Evaluation and Research, adequate samples for the examination of any product or ingredient used in its manufacture,
(f) Bring to the attention of the manufacturer any fault observed in the course of inspection in location, construction, manufacturing methods, or administration of a licensed establishment which might lead to impairment of a product,
(g) Inspect and copy, as circumstances may require, any records required to be kept pursuant to §600.12,
(h) Certify as to the condition of the establishment and of the manufacturing methods followed and make recommendations as to action deemed appropriate with respect to any application for license or any license previously issued.

Subpart D--Reporting of Adverse Experiences

§600.80 Postmarketing reporting of adverse experiences.
(a) Definitions. The following definitions of terms apply to this section:
   Adverse experience: Any adverse event associated with the use of a biological product in humans, whether or not considered product related, including the following: An adverse event occurring in the course of the use of a biological product in professional practice; an adverse event occurring from overdose of the product whether accidental or intentional; an adverse event occurring from abuse of the product; an adverse event occurring from withdrawal of the product; and any failure of expected pharmacological action.
   Blood Component: As defined in §606.3(c) of this chapter.
   Disability: A substantial disruption of a person's ability to conduct normal life functions.
   Life-threatening adverse experience: Any adverse experience that places the patient, in the view of the initial reporter, at immediate risk of death from the adverse experience as it occurred, i.e., it does not include an adverse experience that, had it occurred in a more severe form, might have caused death.
Serious adverse experience: Any adverse experience occurring at any dose that results in any of the following outcomes: Death, a life-threatening adverse experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Unexpected adverse experience: Any adverse experience that is not listed in the current labeling for the biological product. This includes events that may be symptomatically and pathophysiologically related to an event listed in the labeling, but differ from the event because of greater severity or specificity. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the labeling only referred to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the labeling only listed cerebral vascular accidents. “Unexpected,” as used in this definition, refers to an adverse experience that has not been previously observed (i.e., included in the labeling) rather than from the perspective of such experience not being anticipated from the pharmacological properties of the pharmaceutical product.

(b) Review of adverse experiences. Any person having a biologics license under §601.20 of this chapter shall promptly review all adverse experience information pertaining to its product obtained or otherwise received by the licensed manufacturer from any source, foreign or domestic, including information derived from commercial marketing experience, postmarketing clinical investigations, postmarketing epidemiological/surveillance studies, reports in the scientific literature, and unpublished scientific papers. Licensed manufacturers are not required to resubmit to FDA adverse product experience reports forwarded to the licensed manufacturer by FDA; licensed manufacturers, however, must submit all followup information on such reports to FDA. Any person subject to the reporting requirements under paragraph (c) of this section shall also develop written procedures for the surveillance, receipt, evaluation, and reporting of postmarketing adverse experiences to FDA.

(c) Reporting requirements. The licensed manufacturer shall report to FDA adverse experience information, as described in this section. The licensed manufacturer shall submit two copies of each report described in this section for nonvaccine biological products, to the Center for Biologics Evaluation and Research (HFM-210), Food and Drug Administration, 1401 Rockville Pike, suite 200 N., Rockville, MD 20852-1448. Submit all vaccine adverse experience reports to: Vaccine Adverse Event Reporting System (VAERS), P.O. Box 1100, Rockville, MD 20849-1100. FDA may waive the requirement for the second copy in appropriate instances.
(1)

(i) Postmarketing 15-day “Alert reports”. The licensed manufacturer shall report each adverse experience that is both serious and unexpected, whether foreign or domestic, as soon as possible but in no case later than 15 calendar days of initial receipt of the information by the licensed manufacturer.

(ii) Postmarketing 15-day “Alert reports”--followup. The licensed manufacturer shall promptly investigate all adverse experiences that are the subject of these postmarketing 15-day Alert reports and shall submit followup reports within 15 calendar days of receipt of new information or as requested by FDA. If additional information is not obtainable, records should be maintained of the unsuccessful steps taken to seek additional information. Postmarketing 15-day Alert reports and followups to them shall be submitted under separate cover.

(iii) Submission of reports. The requirements of paragraphs (c)(1)(i) and (c)(1)(ii) of this section, concerning the submission of postmarketing 15-day Alert reports, shall also apply to any person whose name appears on the label of a licensed biological product as a manufacturer, packer, distributor, shared manufacturer, joint manufacturer, or any other participant involved in divided manufacturing. To avoid unnecessary duplication in the submission to FDA of reports required by paragraphs (c)(1)(i) and (c)(1)(ii) of this section, obligations of persons other than the licensed manufacturer of the final biological product may be met by submission of all reports of serious adverse experiences to the licensed manufacturer of the final product. If a person elects to submit adverse experience reports to the licensed manufacturer of the final product rather than to FDA, the person shall submit each report to the licensed manufacturer of the final product within 5 calendar days of receipt of the report by the person, and the licensed manufacturer of the final product shall then comply with the requirements of this section. Under this circumstance, a person who elects to submit reports to the licensed manufacturer of the final product shall maintain a record of this action which shall include:

(A) A copy of all adverse biological product experience reports submitted to the licensed manufacturer of the final product;

(B) The date the report was received by the person;

(C) The date the report was submitted to the licensed manufacturer of the final product; and-

(D) The name and address of the licensed manufacturer of the final product.

(iv) Report identification. Each report submitted under this paragraph shall bear prominent identification as to its contents, i.e., “15-day Alert report,” or “15-day Alert report-followup.”

(2) Periodic adverse experience reports. (i) The licensed manufacturer shall report each adverse experience not reported under paragraph (c)(1)(i) of this section at quarterly intervals, for 3 years from the date of issuance of the biologics license,
and then at annual intervals. The licensed manufacturer shall submit each quarterly report within 30 days of the close of the quarter (the first quarter beginning on the date of issuance of the biologics license) and each annual report within 60 days of the anniversary date of the issuance of the biologics license. Upon written notice, FDA may extend or reestablish the requirement that a licensed manufacturer submit quarterly reports, or require that the licensed manufacturer submit reports under this section at different times than those stated. Followup information to adverse experiences submitted in a periodic report may be submitted in the next periodic report.

(ii) Each periodic report shall contain:

(A) A narrative summary and analysis of the information in the report and an analysis of the 15-day Alert reports submitted during the reporting interval (all 15-day Alert reports being appropriately referenced by the licensed manufacturer's patient identification number, adverse reaction term(s), and date of submission to FDA);

(B) A form designated for Adverse Experience Reporting by FDA for each adverse experience not reported under paragraph (c)(1)(i) of this section (with an index consisting of a line listing of the licensed manufacturer's patient identification number and adverse reaction term(s)); and

(C) A history of actions taken since the last report because of adverse experiences (for example, labeling changes or studies initiated).

(iii) Periodic reporting, except for information regarding 15-day Alert reports, does not apply to adverse experience information obtained from postmarketing studies (whether or not conducted under an investigational new drug application), from reports in the scientific literature, and from foreign marketing experience.

(d) Scientific literature.

(1) A 15-day Alert report based on information from the scientific literature shall be accompanied by a copy of the published article. The 15-day Alert reporting requirements in paragraph (c)(1)(i) of this section (i.e., serious, unexpected adverse experiences) apply only to reports found in scientific and medical journals either as case reports or as the result of a formal clinical trial.

(2) As with all reports submitted under paragraph (c)(1)(i) of this section, reports based on the scientific literature shall be submitted on the reporting form designated by FDA or comparable format as prescribed by paragraph (f) of this section. In cases where the licensed manufacturer believes that preparing the form designated by FDA constitutes an undue hardship, the licensed manufacturer may arrange with the Division of Biostatistics and Epidemiology (HFM-210) for an acceptable alternative reporting format.

(e) Postmarketing studies.

(1) Licensed manufacturers are not required to submit a 15-day Alert report under paragraph (c) of this section for an adverse experience obtained from a postmarketing clinical study (whether or not conducted under a biological investigational new drug application) unless the licensed manufacturer
concludes that there is a reasonable possibility that the product caused the adverse experience.

(2) The licensed manufacturer shall separate and clearly mark reports of adverse experiences that occur during a postmarketing study as being distinct from those experiences that are being reported spontaneously to the licensed manufacturer.

(f) Reporting forms.

(1) Except as provided in paragraph (f)(3) of this section, the licensed manufacturer shall complete the reporting form designated by FDA for each report of an adverse experience (FDA Form 3500A, or, for vaccines, a VAERS form; foreign events including those associated with the use of vaccines, may be submitted either on an FDA Form 3500A or, if preferred, on a CIOMS I form).

(2) Each completed form should refer only to an individual patient or single attached publication.

(3) Instead of using a designated reporting form, a licensed manufacturer may use a computer-generated form or other alternative format (e.g., a computer-generated tape or tabular listing) provided that:

(i) The content of the alternative format is equivalent in all elements of information to those specified in the form designated by FDA; and

(ii) the format is approved in advance by MEDWATCH: The FDA Medical Products Reporting Program; or, for alternatives to the VAERS Form, by the Division of Biostatistics and Epidemiology.

(4) Copies of the reporting form designated by FDA (FDA-3500A) for nonvaccine biological products may be obtained from the Center for Biologics Evaluation and Research (address above). Additional supplies of the form may be obtained from the Consolidated Forms and Publications Distribution Center, 3222 Hubbard Rd., Landover, MD 20785. Supplies of the VAERS form may be obtained from VAERS by calling 1-800-822-7967.

(g) Multiple reports. A licensed manufacturer should not include in reports under this section any adverse experience that occurred in clinical trials if they were previously submitted as part of the biologics license application. If a report refers to more than one biological product marketed by a licensed manufacturer, the licensed manufacturer should submit the report to the biologics license application for the product listed first in the report.

(h) Patient privacy. For nonvaccine biological products, a licensed manufacturer should not include in reports under this section the names and addresses of individual patients; instead, the licensed manufacturer should assign a unique code number to each report, preferably not more than eight characters in length. The licensed manufacturer should include the name of the reporter from whom the information was received. The names of patients, health care professionals, hospitals, and geographical identifiers in adverse experience reports are not releasable to the public under FDA's public information regulations in part 20 this of chapter. For vaccine adverse experience reports, these data will become part of the CDC Privacy Act System 09-20-0136, “Epidemiologic Studies and Surveillance of Disease Problems.” Information identifying the person who received the vaccine or that person's legal representative will not be made available to the public, but may be available to the vaccinee or legal representative.
(i) Recordkeeping. The licensed manufacturer shall maintain for a period of 10 years records of all adverse experiences known to the licensed manufacturer, including raw data and any correspondence relating to the adverse experiences.

(j) Revocation of biologics license. If a licensed manufacturer fails to establish and maintain records and make reports required under this section with respect to a licensed biological product, FDA may revoke the biologics license for such a product in accordance with the procedures of §601.5 of this chapter.

(k) Exemptions. Manufacturers of the following listed products are not required to submit adverse experience reports under this section:
(1) Whole blood or components of whole blood.
(2) In vitro diagnostic products, including assay systems for the detection of antibodies or antigens to retroviruses. These products are subject to the reporting requirements for devices.

(l) Disclaimer. A report or information submitted by a licensed manufacturer under this section (and any release by FDA of that report or information) does not necessarily reflect a conclusion by the licensed manufacturer or FDA that the report or information constitutes an admission that the biological product caused or contributed to an adverse effect. A licensed manufacturer need not admit, and may deny, that the report or information submitted under this section constitutes an admission that the biological product caused or contributed to an adverse effect. For purposes of this provision, this paragraph also includes any person reporting under paragraph (c)(1)(iii) of this section.

§600.81 Distribution reports.
The licensed manufacturer shall submit information about the quantity of the product distributed under the biologics license, including the quantity distributed to distributors. The interval between distribution reports shall be 6 months. Upon written notice, FDA may require that the licensed manufacturer submit distribution reports under this section at times other than every 6 months. The distribution report shall consist of the bulk lot number (from which the final container was filled), the fill lot numbers for the total number of dosage units of each strength or potency distributed (e.g., fifty thousand per 10-milliliter vials), the label lot number (if different from fill lot number), labeled date of expiration, number of doses in fill lot/label lot, date of release of fill lot/label lot for distribution at that time. If any significant amount of a fill lot/label lot is returned, include this information. Disclosure of financial or pricing data is not required. As needed, FDA may require submission of more detailed product distribution information. Upon written notice, FDA may require that the licensed manufacturer submit reports under this section at times other than those stated. Requests by a licensed manufacturer to submit reports at times other than those stated should be made as a request for a waiver under §600.90.

§600.90 Waivers.
(a) A licensed manufacturer may ask the Food and Drug Administration to waive under this section any requirement that applies to the licensed manufacturer under §§600.80 and 600.81. A waiver request under this section is required to be submitted with supporting documentation. The waiver request is required to contain one of the following:
(1) An explanation why the licensed manufacturer's compliance with the requirement is unnecessary or cannot be achieved,
(2) A description of an alternative submission that satisfies the purpose of the requirement, or
(3) Other information justifying a waiver.
(b) FDA may grant a waiver if it finds one of the following:
(1) The licensed manufacturer's compliance with the requirement is unnecessary or cannot be achieved,
(2) The licensed manufacturer's alternative submission satisfies the requirement, or
(3) The licensed manufacturer's submission otherwise justifies a waiver.
Subpart A--General Provisions

§601.2 Applications for biologics licenses; procedures for filing.
(a) General. To obtain a biologics license under section 351 of the Public Health Service Act for any biological product, the manufacturer shall submit an application to the Director, Center for Biologics Evaluation and Research, on forms prescribed for such purposes, and shall submit data derived from nonclinical laboratory and clinical studies which demonstrate that the manufactured product meets prescribed requirements of safety, purity, and potency; with respect to each nonclinical laboratory study, either a statement that the study was conducted in compliance with the requirements set forth in part 58 of this chapter, or, if the study was not conducted in compliance with such regulations, a brief statement of the reason for the noncompliance; statements regarding each clinical investigation involving human subjects contained in the application, that it either was conducted in compliance with the requirements for institutional review set forth in part 56 of this chapter; or was not subject to such requirements in accordance with §56.104 or §56.105, and was conducted in compliance with requirements for informed consent set forth in part 50 of this chapter. A full description of manufacturing methods; data establishing stability of the product through the dating period; sample(s) representative of the product for introduction or delivery for introduction into interstate commerce; summaries of results of tests performed on the lot(s) represented by the submitted sample(s); specimens of the labels, enclosures, and containers, and if applicable, any Medication Guide required under part 208 of this chapter proposed to be used for the product; and the address of each location involved in the manufacture of the biological product shall be listed in the biologics license application. The applicant shall also include a financial certification or disclosure statement(s) or both for clinical investigators as required by part 54 of this chapter. An application for a biologics license shall not be considered as filed until all pertinent information and data have been received from the manufacturer by the Center for Biologics Evaluation and Research. The applicant shall also include either a claim for categorical exclusion under §25.30 or §25.31 of this chapter or an environmental assessment under §25.40 of this chapter. In lieu of the procedures described in this paragraph, applications for radioactive biological products shall be handled as set forth in paragraph (b) of this section. The applicant, or the applicant's attorney, agent, or other authorized official shall sign the application. An application for any of the following specified categories of biological products subject to licensure shall be handled as set forth in paragraph (c) of this section:
(1) Therapeutic DNA plasmid products;
(2) Therapeutic synthetic peptide products of 40 or fewer amino acids;
(3) Monoclonal antibody products for in vivo use; and
(4) Therapeutic recombinant DNA-derived products.
(b) Radioactive biological products. To obtain marketing approval for a radioactive biological product, as defined in §600.3(ee) of this chapter, the manufacturer of such product shall comply with the following:

(1) An applicant for a radioactive coupled antibody, which means a product that consists of an antibody component coupled with a radionuclide component (or an antibody component intended solely to be coupled with a radionuclide) in which both components provide a pharmacological effect but the biological component determines the site of action, shall submit a biologics license application to the Director, Center for Biologics Evaluation and Research, Food and Drug Administration, except if, as determined by FDA, there are significant scientific issues associated with the radionuclide or other chemically synthesized component, in which case a new drug application shall be submitted to the Center for Drug Evaluation and Research, Food and Drug Administration;

(2) An applicant for a radioactive biological product other than as described in paragraph (b)(1) of this section, shall submit a new drug application to the Center for Drug Evaluation and Research, Food and Drug Administration.

(c)(1) To obtain marketing approval for a biological product subject to licensure which is a therapeutic DNA plasmid product, therapeutic synthetic peptide product of 40 or fewer amino acids, monoclonal antibody product for in vivo use, or therapeutic recombinant DNA-derived product, an applicant shall submit a biologics license application in accordance with paragraph (a) of this section except that the following sections in parts 600 through 680 of this chapter shall not be applicable to such products: §§600.10(b) and (c), 600.11, 600.12, 600.13, 610.11, 610.53, and 610.62 of this chapter.

(2) To the extent that the requirements in this paragraph (c) conflict with other requirements in this subchapter (except for those products described in paragraph (b) of this section for which a new drug application is required), this paragraph (c) shall supersede other requirements.

(d) Approval of a biologics license application or issuance of a biologics license shall constitute a determination that the establishment(s) and the product meet applicable requirements to ensure the continued safety, purity, and potency of such products. Applicable requirements for the maintenance of establishments for the manufacture of a product subject to this section shall include but not be limited to the good manufacturing practice requirements set forth in parts 210, 211, 600, 606, and 820 of this chapter.

(e) Any establishment and product license for a biological product issued under section 351 of the Public Health Service Act (42 U.S.C. 201 et seq.) that has not been revoked or suspended as of December 20, 1999, shall constitute an approved biologics license application in effect under the same terms and conditions set forth in such product license and such portions of the establishment license relating to such product.

[64 FR 56450, Oct. 20, 1999]

§601.4 Issuance and denial of license.

(a) A biologics license shall be issued upon a determination by the Director, Center for Biologics Evaluation and Research that the establishment(s) and the product meet the
applicable requirements established in this chapter. A biologics license shall be valid until suspended or revoked.

(b) If the Commissioner determines that the establishment or product does not meet the requirements established in this chapter, the biologics license application shall be denied and the applicant shall be informed of the grounds for, and of an opportunity for a hearing on, the decision. If the applicant so requests, the Commissioner shall issue a notice of opportunity for hearing on the matter pursuant to §12.21(b) of this chapter.


§601.5 Revocation of license.

(a) A biologics license shall be revoked upon application of the manufacturer giving notice of intention to discontinue the manufacture of all products manufactured under such license or to discontinue the manufacture of a particular product for which a license is held and waiving an opportunity for a hearing on the matter.

(b)(1) The Commissioner shall notify the licensed manufacturer of the intention to revoke the biologics license, setting forth the grounds for, and offering an opportunity for a hearing on the proposed revocation if the Commissioner finds any of the following:

(i) Authorized Food and Drug Administration employees after reasonable efforts have been unable to gain access to an establishment or a location for the purpose of carrying out the inspection required under §600.21 of this chapter,

(ii) Manufacturing of products or of a product has been discontinued to an extent that a meaningful inspection or evaluation cannot be made,

(iii) The manufacturer has failed to report a change as required by §601.12 of this chapter,

(iv) The establishment or any location thereof, or the product for which the license has been issued, fails to conform to the applicable standards established in the license and in this chapter designed to ensure the continued safety, purity, and potency of the manufactured product,

(v) The establishment or the manufacturing methods have been so changed as to require a new showing that the establishment or product meets the requirements established in this chapter in order to protect the public health, or

(vi) The licensed product is not safe and effective for all of its intended uses or is misbranded with respect to any such use.

(2) Except as provided in §601.6 of this chapter, or in cases involving willfulness, the notification required in this paragraph shall provide a reasonable period for the licensed manufacturer to demonstrate or achieve compliance with the requirements of this chapter, before proceedings will be instituted for the revocation of the license. If compliance is not demonstrated or achieved and the licensed manufacturer does not waive the opportunity for a hearing, the Commissioner shall issue a notice of opportunity for hearing on the matter under §12.21(b) of this chapter.
§601.6 Suspension of license.
(a) Whenever the Commissioner has reasonable grounds to believe that any of the grounds for revocation of a license exist and that by reason thereof there is a danger to health, the Commissioner may notify the licensed manufacturer that the biologics license is suspended and require that the licensed manufacturer do the following:
(1) Notify the selling agents and distributors to whom such product or products have been delivered of such suspension, and
(2) Furnish to the Director, Center for Biologics Evaluation and Research, complete records of such deliveries and notice of suspension.
(b) Upon suspension of a license, the Commissioner shall either:
(1) Proceed under the provisions of §601.5(b) of this chapter to revoke the license, or
(2) If the licensed manufacturer agrees, hold revocation in abeyance pending resolution of the matters involved.

§601.7 Procedure for hearings.
(a) A notice of opportunity for hearing, notice of appearance and request for hearing, and grant or denial of hearing for a biological drug pursuant to this part, for which the exemption from the Federal Food, Drug, and Cosmetic Act in §310.4 of this chapter has been revoked, shall be subject to the provisions of §314.200 of this chapter except to the extent that the notice of opportunity for hearing on the matter issued pursuant to §12.21(b) of this chapter specifically provides otherwise.
(b) Hearings pursuant to §§601.4 through 601.6 shall be governed by part 12 of this chapter.
(c) When a license has been suspended pursuant to §601.6 and a hearing request has been granted, the hearing shall proceed on an expedited basis.

§601.8 Publication of revocation.
Notice of revocation of a license, with statement of the cause therefor, shall be issued by the Commissioner and published in the Federal Register.

§601.9 Licenses; reissuance.
(a) Compliance with requirements. A biologics license, previously suspended or revoked, may be reissued or reinstated upon a showing of compliance with requirements and upon such inspection and examination as may be considered necessary by the Director, Center for Biologics Evaluation and Research.
(b) Exclusion of noncomplying location. A biologics license, excluding a location or locations that fail to comply with the requirements in this chapter, may be issued
without further application and concurrently with the suspension or revocation of the license for noncompliance at the excluded location or locations.

(c) Exclusion of noncomplying product(s). In the case of multiple products included under a single biologics license application, a biologics license may be issued, excluding the noncompliant product(s), without further application and concurrently with the suspension or revocation of the biologics license for a noncompliant product(s).

[64 FR 56451, Oct. 20, 1999]

Subpart B [Reserved]

Subpart C--Biologics Licensing

§601.12 Changes to an approved application.

(a) General. As provided by this section, an applicant shall inform Food and Drug Administration (FDA) about each change in the product, production process, quality controls, equipment, facilities, responsible personnel, or labeling, established in the approved license application(s). Before distributing a product made using a change, an applicant shall demonstrate through appropriate validation and/or other clinical and/or non-clinical laboratory studies, the lack of adverse effect of the change on the identity, strength, quality, purity, or potency of the product as they may relate to the safety or effectiveness of the product.

(b) Changes requiring supplement submission and approval prior to distribution of the product made using the change (major changes).

(1) A supplement shall be submitted for any change in the product, production process, quality controls, equipment, facilities, or responsible personnel that has substantial potential to have an adverse effect on the identity, strength, quality, purity, or potency of the product as they may relate to the safety or effectiveness of the product.

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

(i) Changes in the qualitative or quantitative formulation or other specifications as provided in the approved application or in the regulations;

(ii) Changes requiring completion of an appropriate human study to demonstrate the equivalence of the identity, strength, quality, purity, or potency of the product as they may relate to the safety or effectiveness of the product;

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

(iv) Changes in the source material or cell line;

(v) Establishment of a new master cell bank or seed; and

(vi) Changes which may affect product sterility assurance, such as changes in product or component sterilization method(s), or an addition, deletion, or substitution of steps in an aseptic processing operation.

(3) The applicant must obtain approval of the supplement from FDA prior to distribution of the product made using the change. Except for submissions under paragraph (e) of this section, the following shall be contained in the supplement:
(i) A detailed description of the proposed change;
(ii) The product(s) involved;
(iii) The manufacturing site(s) or area(s) affected;
(iv) A description of the methods used and studies performed to evaluate the
effect of the change on the identity, strength, quality, purity, or potency of
the product as they may relate to the safety or effectiveness of the product;
(v) The data derived from such studies;
(vi) Relevant validation protocols and data; and
(vii) A reference list of relevant standard operating procedures
(SOP's).

(c) Changes requiring supplement submission at least 30 days prior to distribution of the
product made using the change.

(1) A supplement shall be submitted for any change in the product, production
process, quality controls, equipment, facilities, or responsible personnel that has
a moderate potential to have an adverse effect on the identity, strength, quality,
purity, or potency of the product as they may relate to the safety or effectiveness
of the product. The supplement shall be labeled “Supplement--Changes Being
Effected in 30 Days” or, if applicable under paragraph (c)(5) of this section,
“Supplement--Changes Being Effected.”

(2) These changes include, but are not limited to:
(i) Change in the site of testing from one facility to another;
(ii) An increase or decrease in production scale during finishing steps that
involves new or different equipment; and
(iii) Replacement of equipment with that of similar, but not identical, design and
operating principle that does not affect the process methodology or
process operating parameters.

(3) Pending approval of the supplement by FDA, and except as provided in paragraph
(c)(5) of this section, distribution of the product made using the change may begin not
less than 30 days after receipt of the supplement by FDA. The information listed in
paragraph (b)(3)(i) through (b)(3)(vii) of this section shall be contained in the
supplement.

(4) If within 30 days following FDA's receipt of the supplement, FDA informs the
applicant that either:
(i) The change requires approval prior to distribution of the product in
accordance with paragraph (b) of this section; or
(ii) Any of the information required under paragraph (c)(3) of this section is
missing; the applicant shall not distribute the product made using the
change until FDA determines that compliance with this section is
achieved.

(5) In certain circumstances, FDA may determine that, based on experience with a
particular type of change, the supplement for such change is usually complete
and provides the proper information, and on particular assurances that the
proposed change has been appropriately submitted, the product made using the
change may be distributed immediately upon receipt of the supplement by FDA.
These circumstances may include substantial similarity with a type of change
regularly involving a “Supplement--Changes Being Effected” supplement or a

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situation in which the applicant presents evidence that the proposed change has been validated in accordance with an approved protocol for such change under paragraph (e) of this section.

(d) Changes to be described in an annual report (minor changes).

(1) Changes in the product, production process, quality controls, equipment, facilities, or responsible personnel that have a minimal potential to have an adverse effect on the identity, strength, quality, purity, or potency of the product as they may relate to the safety or effectiveness of the product shall be documented by the applicant in an annual report submitted each year within 60 days of the anniversary date of approval of the application. The Director, Center for Biologics Evaluation and Research, may approve a written request for an alternative date to combine annual reports for multiple approved applications into a single annual report submission.

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

(i) Any change made to comply with an official compendium that is consistent with FDA requirements;

(ii) The deletion of an ingredient intended only to affect the color of the product except that a change intended only to affect Blood Grouping Reagents requires supplement submission and approval prior to distribution of the product made using the change in accordance with the requirements set forth in paragraph (b) of this section;

(iii) An extension of an expiration date based upon full shelf-life data obtained from a protocol approved in the application;

(iv) A change within the container and closure system for solid dosage forms, based upon a showing of equivalency to the approved system under a protocol approved in the application or published in an official compendium;

(v) A change in the size of a container for a solid dosage form, without a change from one container and closure system to another;

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

(vii) The addition or deletion of an alternate analytical method.

(3) The following information for each change shall be contained in the annual report:

(i) A list of all products involved; and

(ii) A full description of the manufacturing and controls changes including: the manufacturing site(s) or area(s) involved; the date the change was made; a cross-reference to relevant validation protocols and/or SOP’s; and relevant data from studies and tests performed to evaluate the effect of the change on the identity, strength, quality, purity, or potency of the product as they may relate to the safety or effectiveness of the product.

(4) The applicant shall submit the report to the FDA office responsible for reviewing the application. The report shall include all the information required under this paragraph for each change made during the annual reporting interval which ends on the anniversary date in the order in which they were implemented.
(e) An applicant may submit one or more protocols describing the specific tests and validation studies and acceptable limits to be achieved to demonstrate the lack of adverse effect for specified types of manufacturing changes on the identity, strength, quality, purity, or potency of the product as they may relate to the safety or effectiveness of the product. Any such protocols, or change to a protocol, shall be submitted as a supplement requiring approval from FDA prior to distribution of the product which, if approved, may justify a reduced reporting category for the particular change because the use of the protocol for that type of change reduces the potential risk of an adverse effect.

(f) Labeling changes.

(1) Labeling changes requiring supplement submission--FDA approval must be obtained before distribution of the product with the labeling change. Except as described in paragraphs (f)(2) and (f)(3) of this section, an applicant shall submit a supplement describing a proposed change in the package insert, package label, container label, or, if applicable, a Medication Guide required under part 208 of this chapter, and include the information necessary to support the proposed change. The supplement shall clearly highlight the proposed change in the labeling. The applicant shall obtain approval from FDA prior to distribution of the product with the labeling change.

(2) Labeling changes requiring supplement submission--product with a labeling change that may be distributed before FDA approval.

(i) An applicant shall submit, at the time such change is made, a supplement for any change in the package insert, package label, or container label to accomplish any of the following:

(A) To add or strengthen a contraindication, warning, precaution, or adverse reaction;

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

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

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

(ii) Pending approval of the supplement by FDA, the applicant may distribute a product with a package insert, package label, or container label bearing such change at the time the supplement is submitted. The supplement shall clearly identify the change being made and include necessary supporting data. The supplement and its mailing cover shall be plainly marked: “Special Labeling Supplement--Changes Being Effected.”

(3) Labeling changes requiring submission in an annual report. (i) An applicant shall submit any final printed package insert, package label, or Medication Guide required under part 208 of this chapter incorporating the following changes in an annual report submitted to FDA each year as provided in paragraph (d)(1) of this section:

(A) Editorial or similar minor changes;

(B) A change in the information on how the product is supplied that does not involve a change in the dosage strength or dosage form; and
(C) A change in the information specified in §208.20(b)(8)(iii) and (b)(8)(iv) of this chapter for a Medication Guide.

(ii) The applicant may distribute a product with a package insert, package label, or container label bearing such change at the time the change is made.

(4) Advertisements and promotional labeling. Advertisements and promotional labeling shall be submitted to the Center for Biologics Evaluation and Research in accordance with the requirements set forth in §314.81(b)(3)(i) of this chapter, except that Form FDA-2567 (Transmittal of Labels and Circulars) or an equivalent form shall be used.

(g) Failure to comply. In addition to other remedies available in law and regulations, in the event of repeated failure of the applicant to comply with this section, FDA may require that the applicant submit a supplement for any proposed change and obtain approval of the supplement by FDA prior to distribution of the product made using the change.

(h) Administrative review. Under §10.75 of this chapter, an applicant may request internal FDA review of FDA employee decisions under this section.


§601.15 Foreign establishments and products: samples for each importation.

Random samples of each importation, obtained by the District Director of Customs and forwarded to the Director, Center for Biologics Evaluation and Research, shall be at least two final containers of each lot of product. A copy of the associated documents which describe and identify the shipment shall accompany the shipment for forwarding with the samples to the Director, Center for Biologics Evaluation and Research. For shipments of 20 or less final containers, samples need not be forwarded, provided a copy of an official release from the Center for Biologics Evaluation and Research accompanies each shipment.


§601.20 Biologics licenses; issuance and conditions.

(a) Examination--compliance with requirements. A biologics license application shall be approved only upon examination of the product and upon a determination that the product complies with the standards established in the biologics license application and the requirements prescribed in the regulations in this chapter including but not limited to the good manufacturing practice requirements set forth in parts 210, 211, 600, 606, and 820 of this chapter.

(b) Availability of product. No biologics license shall be issued unless:

(1) The product intended for introduction into interstate commerce is available for examination, and

(2) Such product is available for inspection during all phases of manufacture.

(c) Manufacturing process--impairment of assurances. No product shall be licensed if any part of the process of or relating to the manufacture of such product, in the judgment
of the Director, Center for Biologics Evaluation and Research, would impair the assurances of continued safety, purity, and potency as provided by the regulations contained in this chapter.

(d) Inspection--compliance with requirements. A biologics license shall be issued or a biologics license application approved only after inspection of the establishment(s) listed in the biologics license application and upon a determination that the establishment(s) complies with the standards established in the biologics license application and the requirements prescribed in applicable regulations.

(e) One biologics license to cover all locations. One biologics license shall be issued to cover all locations meeting the establishment standards identified in the approved biologics license application and each location shall be subject to inspection by FDA officials.

[64 FR 56451, Oct. 20, 1999]

§601.21 Products under development.
A biological product undergoing development, but not yet ready for a biologics license, may be shipped or otherwise delivered from one State or possession into another State or possession provided such shipment or delivery is not for introduction or delivery for introduction into interstate commerce, except as provided in sections 505(i) and 520(g) of the Federal Food, Drug, and Cosmetic Act, as amended, and the regulations thereunder (21 CFR parts 312 and 812).

[64 FR 56451, Oct. 20, 1999]

§601.22 Products in short supply; initial manufacturing at other than licensed location.
A biologics license issued to a manufacturer and covering all locations of manufacture shall authorize persons other than such manufacturer to conduct at places other than such locations the initial, and partial manufacturing of a product for shipment solely to such manufacturer only to the extent that the names of such persons and places are registered with the Commissioner of Food and Drugs and it is found upon application of such manufacturer, that the product is in short supply due either to the peculiar growth requirements of the organism involved or to the scarcity of the animal required for manufacturing purposes, and such manufacturer has established with respect to such persons and places such procedures, inspections, tests or other arrangements as will ensure full compliance with the applicable regulations of this subchapter related to continued safety, purity, and potency. Such persons and places shall be subject to all regulations of this subchapter except §§601.2 to 601.6, 601.9, 601.10, 601.20, 601.21 to 601.33, and 610.60 to 610.65 of this chapter. For persons and places authorized under this section to conduct the initial and partial manufacturing of a product for shipment solely to a manufacturer of a product subject to licensure under §601.2(c), the following additional regulations shall not be applicable: §§600.10(b) and (c), 600.11, 600.12, 600.13, 610.11, and 610.53 of this chapter. Failure of such manufacturer to maintain such procedures, inspections, tests, or other arrangements, or failure of any person conducting such partial manufacturing to comply with applicable regulations shall constitute a ground for suspension or revocation of the authority conferred pursuant to this section on
the same basis as provided in §§601.6 to 601.8 with respect to the suspension and the revocation of licenses.


§601.25 Review procedures to determine that licensed biological products are safe, effective, and not misbranded under prescribed, recommended, or suggested conditions of use.

For purposes of reviewing biological products that have been licensed prior to July 1, 1972, to determine that they are safe and effective and not misbranded, the following regulations shall apply. Prior administrative action exempting biological products from the provisions of the Federal Food, Drug, and Cosmetic Act is superseded to the extent that these regulations result in imposing requirements pursuant to provisions therein for a designated biological product or category of products.

(a) Advisory review panels. The Commissioner of Food and Drugs shall appoint advisory review panels

(1) to evaluate the safety and effectiveness of biological products for which a license has been issued pursuant to section 351 of the Public Health Service Act,

(2) to review the labeling of such biological products, and

(3) to advise him on which of the biological products under review are safe, effective, and not misbranded. An advisory review panel shall be established for each designated category of biological product. The members of a panel shall be qualified experts, appointed by the Commissioner, and shall include persons from lists submitted by organizations representing professional, consumer, and industry interests. Such persons shall represent a wide divergence of responsible medical and scientific opinion. The Commissioner shall designate the chairman of each panel, and summary minutes of all meetings shall be made.

(b) Request for data and views.

(1) The Commissioner of Food and Drugs will publish a notice in the Federal Register requesting interested persons to submit, for review and evaluation by an advisory review panel, published and unpublished data and information pertinent to a designated category of biological products.

(2) Data and information submitted pursuant to a published notice, and falling within the confidentiality provisions of 18 U.S.C. 1905, 5 U.S.C. 552(b), or 21 U.S.C. 331(j), shall be handled by the advisory review panel and the Food and Drug Administration as confidential until publication of a proposed evaluation of the biologics under review and the full report or reports of the panel. Thirty days thereafter such data and information shall be made publicly available and may be viewed at the Dockets Management Branch of the Food and Drug Administration, except to the extent that the person submitting it demonstrates that it still falls within the confidentiality provisions of one or more of those statutes.

(3) To be considered, 12 copies of the submission on any marketed biological product within the class shall be submitted, preferably bound, indexed, and on standard sized paper, approximately 8\1/2\ x 11 inches. The time allotted for submissions will be 60 days, unless otherwise indicated in the specific notice requesting data.
and views for a particular category of biological products. When requested, abbreviated submissions should be sent. All submissions shall be in the following format, indicating “none” or “not applicable” where appropriate, unless changed in the Federal Register notice: Biological Products Review Information

I. Label or labels and all other labeling (preferably mounted. Facsimile labeling is acceptable in lieu of actual container labeling), including labeling for export.

II. Representative advertising used during the past 5 years.

III. The complete quantitative composition of the biological product.

IV. Animal safety data.
   A. Individual active components.
      1. Controlled studies.
      2. Partially controlled or uncontrolled studies.
   B. Combinations of the individual active components.
      1. Controlled studies.
      2. Partially controlled or uncontrolled studies.
   C. Finished biological product.
      1. Controlled studies.
      2. Partially controlled or uncontrolled studies.

V. Human safety data.
   A. Individual active components.
      1. Controlled studies.
      2. Partially controlled or uncontrolled studies.
      3. Documented case reports.
      4. Pertinent marketing experiences that may influence a determination as to the safety of each individual active component.
      5. Pertinent medical and scientific literature.
   B. Combinations of the individual active components.
      1. Controlled studies.
      2. Partially controlled or uncontrolled studies.
      3. Documented case reports.
      4. Pertinent marketing experiences that may influence a determination as to the safety of combinations of the individual active components.
      5. Pertinent medical and scientific literature.
   C. Finished biological product.
      1. Controlled studies.
      2. Partially controlled or uncontrolled studies.
      3. Documented case reports.
      4. Pertinent marketing experiences that may influence a determination as to the safety of the finished biological product.
      5. Pertinent medical and scientific literature.

VI. Efficacy data.
   A. Individual active components.
      1. Controlled studies.
2. Partially controlled or uncontrolled studies.
3. Documented case reports.
4. Pertinent marketing experiences that may influence a determination on the efficacy of each individual active component.
5. Pertinent medical and scientific literature.

B. Combinations of the individual active components.
1. Controlled studies.
2. Partially controlled or uncontrolled studies.
3. Documented case reports.
4. Pertinent marketing experiences that may influence a determination as to the effectiveness of combinations of the individual active components.
5. Pertinent medical and scientific literature.

C. Finished biological product.
1. Controlled studies.
2. Partially controlled or uncontrolled studies.
3. Documented case reports.
4. Pertinent marketing experiences that may influence a determination as to the effectiveness of the finished biological product.
5. Pertinent medical and scientific literature.

VII. A summary of the data and views setting forth the medical rational and purpose (or lack thereof) for the biological product and its components and the scientific basis (or lack thereof) for the conclusion that the biological product, including its components, has been proven safe and effective and is properly labeled for the intended use or uses. If there is an absence of controlled studies in the materials submitted, an explanation as to why such studies are not considered necessary or feasible shall be included.

VIII. If the submission is by a licensed manufacturer, a statement signed by the authorized official of the licensed manufacturer shall be included, stating that to the best of his or her knowledge and belief, it includes all information, favorable and unfavorable, pertinent to an evaluation of the safety, effectiveness, and labeling of the product, including information derived from investigation, commercial marketing, or published literature. If the submission is by an interested person other than a licensed manufacturer, a statement signed by the person responsible for such submission shall be included, stating that to the best of his knowledge and belief, it fairly reflects a balance of all the available information, favorable and unfavorable available to him, pertinent to an evaluation of the safety, effectiveness, and labeling of the product.

(c) Deliberations of an advisory review panel. An advisory review panel will meet as often and for as long as is appropriate to review the data submitted to it and to prepare a report containing its conclusions and recommendations to the Commissioner of Food and Drugs with respect to the safety, effectiveness, and labeling of the biological products in the designated category under review.

(1) A panel may also consult any individual or group.
(2) Any interested person may request in writing an opportunity to present oral views to the panel. Such written requests for oral presentations should include a summarization of the data to be presented to the panel. Such request may be granted or denied by the panel.

(3) Any interested person may present written data and views which shall be considered by the panel. This information shall be presented to the panel in the format set forth in paragraph (b)(3) of this section and within the time period established for the biological product category in the notice for review by a panel.

(d) Standards for safety, effectiveness, and labeling. The advisory review panel, in reviewing the submitted data and preparing the panel's conclusions and recommendations, and the Commissioner of Food and Drugs, in reviewing and implementing the conclusions and recommendations of the panel, shall apply the following standards to determine that a biological product is safe and effective and not misbranded.

(1) **Safety** means the relative freedom from harmful effect to persons affected, directly or indirectly, by a product when prudently administered, taking into consideration the character of the product in relation to the condition of the recipient at the time. Proof of safety shall consist of adequate tests by methods reasonably applicable to show the biological product is safe under the prescribed conditions of use, including results of significant human experience during use.

(2) **Effectiveness** means a reasonable expectation that, in a significant proportion of the target population, the pharmacological or other effect of the biological product, when used under adequate directions, for use and warnings against unsafe use, will serve a clinically significant function in the diagnosis, cure, mitigation, treatment, or prevention of disease in man. Proof of effectiveness shall consist of controlled clinical investigations as defined in §314.126 of this chapter, unless this requirement is waived on the basis of a showing that it is not reasonably applicable to the biological product or essential to the validity of the investigation, and that an alternative method of investigation is adequate to substantiate effectiveness. Alternate methods, such as serological response evaluation in clinical studies and appropriate animal and other laboratory assay evaluations may be adequate to substantiate effectiveness where a previously accepted correlation between data generated in this way and clinical effectiveness already exists. Investigations may be corroborated by partially controlled or uncontrolled studies, documented clinical studies by qualified experts, and reports of significant human experience during marketing. Isolated case reports, random experience, and reports lacking the details which permit scientific evaluation will not be considered.

(3) The benefit-to-risk ratio of a biological product shall be considered in determining safety and effectiveness.

(4) A biological product may combine two or more safe and effective active components:

(i) When each active component makes a contribution to the claimed effect or effects;
(ii) when combining of the active ingredients does not decrease the purity, potency, safety, or effectiveness of any of the individual active components; and
(iii) if the combination, when used under adequate directions for use and warnings against unsafe use, provides rational concurrent preventive therapy or treatment for a significant proportion of the target population.

(5) Labeling shall be clear and truthful in all respects and may not be false or misleading in any particular. It shall comply with section 351 of the Public Health Service Act and sections 502 and 503 of the Federal Food, Drug, and Cosmetic Act, and in particular with the applicable requirements of §§610.60 through 610.65 and subpart D of part 201 of this chapter.

(e) Advisory review panel report to the Commissioner. An advisory review panel shall submit to the Commissioner of Food and Drugs a report containing the panel's conclusions and recommendations with respect to the biological products falling within the category covered by the panel. Included within this report shall be:

(1) A statement which designates those biological products determined by the panel to be safe and effective and not misbranded. This statement may include any condition relating to active components, labeling, tests required prior to release of lots, product standards, or other conditions necessary or appropriate for their safety and effectiveness.

(2) A statement which designates those biological products determined by the panel to be unsafe or ineffective, or to be misbranded. The statement shall include the panel's reasons for each such determination.

(3) A statement which designates those biological products determined by the panel not to fall within either paragraph (e) (1) or (2) of this section on the basis of the panel's conclusion that the available data are insufficient to classify such biological products, and for which further testing is therefore required. The report shall recommend with as much specificity as possible the type of further testing required and the time period within which it might reasonably be concluded. The report shall also recommend whether the product license should or should not be revoked, thus permitting or denying continued manufacturing and marketing of the biological product pending completion of the testing. This recommendation will be based on an assessment of the present evidence of the safety and effectiveness of the product and the potential benefits and risks likely to result from the continued use of the product for a limited period of time while the questions raised concerning the product are being resolved by further study.

As of November 4 1982 the provisions under paragraphs (e)(3) and (f)(3) of this section for the interim marketing of certain biological products pending completion of additional studies have been superseded by the review and reclassification procedures under §601.26 of this chapter. The superseded text is included for the convenience of the user only.

(f) Proposed order. After reviewing the conclusions and recommendations of the advisory review panel, the Commissioner of Food and Drugs shall publish in the Federal Register a proposed order containing:

(1) A statement designating the biological products in the category under review that are determined by the Commissioner of Food and Drugs to be safe and effective
and not misbranded. This statement may include any condition relating to active components, labeling, tests required prior to release of lots, product standards, or other conditions necessary or appropriate for their safety and effectiveness, and may propose corresponding amendments in other regulations under this subchapter F.

(2) A statement designating the biological products in the category under review that are determined by the Commissioner of Food and Drugs to be unsafe or ineffective, or to be misbranded, together with the reasons therefor. All licenses for such products shall be proposed to be revoked.

(3) A statement designating the biological products not included in either of the above two statements on the basis of the Commissioner of Food and Drugs determination that the available data are insufficient to classify such biological products under either paragraph (f) (1) or (2) of this section. Licenses for such products may be proposed to be revoked or to remain in effect on an interim basis. Where the Commissioner determines that the potential benefits outweigh the potential risks, the proposed order shall provide that the biologics license for any biological product, falling within this paragraph, will not be revoked but will remain in effect on an interim basis while the data necessary to support its continued marketing are being obtained for evaluation by the Food and Drug Administration. The tests necessary to resolve whatever safety or effectiveness questions exist shall be described.

As of November 4 1982 the provisions under paragraphs (e)(3) and (f)(3) of this section for the interim marketing of certain biological products pending completion of additional studies have been superseded by the review and reclassification procedures under §601.26 of this chapter. The superseded text is included for the convenience of the user only.

(4) The full report or reports of the panel to the Commissioner of Food and Drugs. The summary minutes of the panel meeting or meetings shall be made available to interested persons upon request. Any interested person may within 90 days after publication of the proposed order in the Federal Register, file with the Hearing Clerk of the Food and Drug Administration written comments in quintuplicate. Comments may be accompanied by a memorandum or brief in support thereof. All comments may be reviewed at the office of the Dockets Management Branch during regular working hours, Monday through Friday.

(g) Final order. After reviewing the comments, the Commissioner of Food and Drugs shall publish in the Federal Register a final order on the matters covered in the proposed order. The final order shall become effective as specified in the order.

(h) [Reserved]

(i) Court Appeal. The final order(s) published pursuant to paragraph (g) of this section, and any notice published pursuant to paragraph (h) of this section, constitute final agency action from which appeal lies to the courts. The Food and Drug Administration will request consolidation of all appeals in a single court. Upon court appeal, the Commissioner of Food and Drugs may, at his discretion, stay the effective date for part or all of the final order or notice, pending appeal and final court adjudication.
§601.26 Reclassification procedures to determine that licensed biological products are safe, effective, and not misbranded under prescribed, recommended, or suggested conditions of use.

This regulation establishes procedures for the reclassification of all biological products that have been classified into Category IIIA. A Category IIIA biological product is one for which an advisory review panel has recommended under §601.25(e)(3), the Commissioner of Food and Drugs (Commissioner) has proposed under §601.25(f)(3), or the Commissioner has finally decided under §601.25(g) that available data are insufficient to determine whether the product license should be revoked or affirmed and which may be marketed pending the completion of further testing. All of these Category IIIA products will either be reclassified into Category I (safe, effective, and not misbranded) or Category II (unsafe, ineffective, or misbranded) in accordance with the procedures set forth below.

(a) Advisory review panels. The Commissioner will appoint advisory review panels and use existing advisory review panels to
   (1) evaluate the safety and effectiveness of all Category IIIA biological products;
   (2) review the labeling of such products; and
   (3) advise the Commissioner on which Category IIIA biological products are safe, effective, and not misbranded. These advisory review panels will be established in accordance with procedures set forth in §601.25(a).

(b) Deliberations of advisory review panels. The deliberations of advisory review panels will be conducted in accordance with §601.25(d).

(c) Advisory review panel report to the Commissioner. An advisory review panel shall submit to the Commissioner a report containing the panel's conclusions and recommendations with respect to the biological products falling within the category of products reviewed by the panel. The panel report shall include:
   (1) A statement designating the biological products in the category under review in accordance with either §601.25(e)(1) or §601.25(e)(2).
   (2) A statement identifying those biological products designated under §601.25(e)(2) that the panel recommends should be designated as safe and presumptively effective and should remain on the market pending completion of further testing because there is a compelling medical need and no suitable alternative therapeutic, prophylactic, or diagnostic agent that is available in sufficient quantities to meet current medical needs. For the products or categories of products so recommended, the report shall include:
      (i) A description and evaluation of the available evidence concerning effectiveness and an explanation why the evidence shows that the product has any benefit; and
      (ii) A description of the alternative therapeutic, prophylactic, or diagnostic agents considered and a statement of why such alternatives are not suitable. In making this recommendation the panel shall also take into account the seriousness of the condition intended to be treated, prevented,
or diagnosed by the product, the risks involved in the continued use of the product, and the likelihood that, based upon existing data, the effectiveness of the product can eventually be established by further testing and new test development. The report shall also recommend with as much specificity as possible the type of further testing required and the time period within which it might reasonably be concluded.

(d) Proposed order. After reviewing the conclusions and recommendations of the advisory review panels, the Commissioner shall publish in the Federal Register a proposed order containing:

(1) A statement designating the biological products in the category under review in accordance with either §601.25(e)(1) or §601.25(e)(2);

(2) A notice of availability of the full panel report or reports. The full panel report or reports shall be made publicly available at the time of publication of the proposed order.

(3) A proposal to accept or reject the findings of the advisory review panel required by §601.26(c)(2)(i) and (ii).

(4) A statement identifying those biological products that the Commissioner proposes should be designated as safe and presumptively effective under §601.26(c)(2) and should be permitted to remain on the market pending completion of further testing because there is a compelling medical need and no suitable alternative therapeutic, prophylactic, or diagnostic agent for the product that is available in sufficient quantities to meet current medical needs. In making this proposal, the Commissioner shall take into account the seriousness of the condition to be treated, prevented, or diagnosed by the product, the risks involved in the continued use of the product, and the likelihood that, based upon existing data, the effectiveness of the product can eventually be established by further testing.

(e) Final order. After reviewing the comments on the proposed order, the Commissioner shall publish in the Federal Register a final order on the matters covered in the proposed order. Where the Commissioner determines that there is a compelling medical need and no suitable alternative therapeutic, prophylactic, or diagnostic agent for any biological product that is available in sufficient quantities to meet current medical needs, the final order shall provide that the biologics license application for that biological product will not be revoked, but will remain in effect on an interim basis while the data necessary to support its continued marketing are being obtained for evaluation by the Food and Drug Administration. The final order shall describe the tests necessary to resolve whatever effectiveness questions exist.

(f) Additional studies and labeling.

(1) Within 60 days following publication of the final order, each licensed manufacturer for a biological product designated as requiring further study to justify continued marketing on an interim basis, under paragraph (e) of this section, shall submit to the Commissioner a written statement intended to show that studies adequate and appropriate to resolve the questions raised about the product have been undertaken. The Federal Government may undertake the studies. Any study involving a clinical investigation that involves human subjects shall be conducted in compliance with the requirements for informed consent under part 50 of this chapter. Such a study is also subject to the
requirements for institutional review under part 56 of this chapter unless exempt under §56.104 or §56.105. The Commissioner may extend this 60-day period if necessary, either to review and act on proposed protocols or upon indication from the licensed manufacturer that the studies will commence at a specified reasonable time. If no such commitment is made, or adequate and appropriate studies are not undertaken, the biologics license or licenses shall be revoked.

(2) A progress report shall be filed on the studies by January 1 and July 1 until completion. If the progress report is inadequate or if the Commissioner concludes that the studies are not being pursued promptly and diligently, or if interim results indicate the product is not a medical necessity, the biologics license or licenses shall be revoked.

(3) Promptly upon completion of the studies undertaken on the product, the Commissioner will review all available data and will either retain or revoke the biologics license or licenses involved. In making this review the Commissioner may again consult the advisory review panel which prepared the report on the product, or other advisory committees, professional organizations, or experts. The Commissioner shall take such action by notice published in the Federal Register.

(4) Labeling and promotional material for those biological products requiring additional studies shall bear a box statement in the following format:

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Based on a review by the (insert name of appropriate advisory review panel) and other information the Food and Drug Administration has directed that further investigation be conducted before this product is conclusively determined to be effective for labeled indication(s).
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(5) A written informed consent shall be obtained from participants in any additional studies required under paragraph (f)(1) of this section, explaining the nature of the product and the investigation. The explanation shall consist of such disclosure and be made so that intelligent and informed consent be given and that a clear opportunity to refuse is presented.

(g) Court appeal. The final order(s) published pursuant to paragraph (e) of this section constitute final agency action from which appeal lies to the courts. The Food and Drug Administration will request consolidation of all appeals in a single court. Upon court appeal, the Commissioner of Food and Drugs may, at the Commissioner's discretion, stay the effective date for part or all of the final order or notice, pending appeal and final court adjudication.

(h) [Reserved]

(i) Institutional review and informed consent. Information and data submitted under this section after July 27, 1981, shall include statements regarding each clinical investigation involving human subjects, that it was conducted in compliance with the requirements for informed consent under part 50 of this chapter. Such a study is also subject to the requirements for institutional review under part 56 of this chapter, unless exempt under §56.104 or §56.105.

§601.27 Pediatric studies.

(a) Required assessment. Except as provided in paragraphs (b), (c), and (d) of this section, each application for a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration shall contain data that are adequate to assess the safety and effectiveness of the product for the claimed indications in all relevant pediatric subpopulations, and to support dosing and administration for each pediatric subpopulation for which the product is safe and effective. Where the course of the disease and the effects of the product are similar in adults and pediatric patients, FDA may conclude that pediatric effectiveness can be extrapolated from adequate and well-controlled effectiveness studies in adults, usually supplemented with other information in pediatric patients, such as pharmacokinetic studies. In addition, studies may not be needed in each pediatric age group, if data from one age group can be extrapolated to another. Assessments required under this section for a product that represents a meaningful therapeutic benefit over existing treatments must be carried out using appropriate formulations for the age group(s) for which the assessment is required.

(b) Deferred submission.

(1) FDA may, on its own initiative or at the request of an applicant, defer submission of some or all assessments of safety and effectiveness described in paragraph (a) of this section until after licensing of the product for use in adults. Deferral may be granted if, among other reasons, the product is ready for approval in adults before studies in pediatric patients are complete, pediatric studies should be delayed until additional safety or effectiveness data have been collected. If an applicant requests deferred submission, the request must provide an adequate justification for delaying pediatric studies, a description of the planned or ongoing studies, and evidence that the studies are being or will be conducted with due diligence and at the earliest possible time.

(2) If FDA determines that there is an adequate justification for temporarily delaying the submission of assessments of pediatric safety and effectiveness, the product may be licensed for use in adults subject to the requirement that the applicant submit the required assessments within a specified time.

(c) Waivers—

(1) General. FDA may grant a full or partial waiver of the requirements of paragraph (a) of this section on its own initiative or at the request of an applicant. A request for a waiver must provide an adequate justification.

(2) Full waiver. An applicant may request a waiver of the requirements of paragraph (a) of this section if the applicant certifies that:

(i) The product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients and is not likely to be used in a substantial number of pediatric patients;

(ii) Necessary studies are impossible or highly impractical because, e.g., the number of such patients is so small or geographically dispersed; or

(iii) There is evidence strongly suggesting that the product would be ineffective or unsafe in all pediatric age groups.
(3) Partial waiver. An applicant may request a waiver of the requirements of paragraph (a) of this section with respect to a specified pediatric age group, if the applicant certifies that:

(i) The product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in that age group, and is not likely to be used in a substantial number of patients in that age group;

(ii) Necessary studies are impossible or highly impractical because, e.g., the number of patients in that age group is so small or geographically dispersed;

(iii) There is evidence strongly suggesting that the product would be ineffective or unsafe in that age group; or

(iv) The applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for that age group have failed.

(4) FDA action on waiver. FDA shall grant a full or partial waiver, as appropriate, if the agency finds that there is a reasonable basis on which to conclude that one or more of the grounds for waiver specified in paragraphs (c)(2) or (c)(3) of this section have been met. If a waiver is granted on the ground that it is not possible to develop a pediatric formulation, the waiver will cover only those pediatric age groups requiring that formulation. If a waiver is granted because there is evidence that the product would be ineffective or unsafe in pediatric populations, this information will be included in the product’s labeling.

(5) Definition of “meaningful therapeutic benefit”. For purposes of this section, a product will be considered to offer a meaningful therapeutic benefit over existing therapies if FDA estimates that:

(i) If approved, the product would represent a significant improvement in the treatment, diagnosis, or prevention of a disease, compared to marketed products adequately labeled for that use in the relevant pediatric population. Examples of how improvement might be demonstrated include, e.g., evidence of increased effectiveness in treatment, prevention, or diagnosis of disease; elimination or substantial reduction of a treatment-limiting drug reaction; documented enhancement of compliance; or evidence of safety and effectiveness in a new subpopulation; or

(ii) The product is in a class of products or for an indication for which there is a need for additional therapeutic options.

(d) Exemption for orphan drugs. This section does not apply to any product for an indication or indications for which orphan designation has been granted under part 316, subpart C, of this chapter.

[63 FR 66671, Dec. 2, 1998]

§601.28 Annual reports of postmarketing pediatric studies.

Sponsors of licensed biological products shall submit the following information each year within 60 days of the anniversary date of approval of the license to the Director, Center for Biologics Evaluation and Research:

(a) Summary. A brief summary stating whether labeling supplements for pediatric use have been submitted and whether new studies in the pediatric population to support appropriate labeling for the pediatric population have been initiated. Where possible,
an estimate of patient exposure to the drug product, with special reference to the pediatric population (neonates, infants, children, and adolescents) shall be provided, including dosage form.

(b) Clinical data. Analysis of available safety and efficacy data in the pediatric population and changes proposed in the labeling based on this information. An assessment of data needed to ensure appropriate labeling for the pediatric population shall be included.

(c) Status reports. A statement on the current status of any postmarketing studies in the pediatric population performed by, or on behalf of, the applicant. The statement shall include whether postmarketing clinical studies in pediatric populations were required or agreed to, and, if so, the status of these studies shall be reported to FDA in annual progress reports of postmarketing studies under §601.70 rather than under this section.


§601.29 Guidance documents.

(a) FDA has made available guidance documents under §10.115 of this chapter to help you comply with certain requirements of this part.

(b) The Center for Biologics Evaluation and Research (CBER) maintains a list of guidance documents that apply to the center's regulations. The lists are maintained on the Internet and are published annually in the Federal Register. You may request a copy of the CBER list from the Office of Communication, Training, and Manufacturers Assistance (HFM-40), Center for Biologics Evaluation and Research, Food and Drug Administration, 1401 Rockville Pike, Rockville, MD 20852-1448.

[65 FR 56480, Sept. 19, 2000]

Subpart D--Diagnostic Radiopharmaceuticals

§601.30 Scope.

Source: 64 FR 26668, May 17, 1999, unless otherwise noted.

This subpart applies to radiopharmaceuticals intended for in vivo administration for diagnostic and monitoring use. It does not apply to radiopharmaceuticals intended for therapeutic purposes. In situations where a particular radiopharmaceutical is proposed for both diagnostic and therapeutic uses, the radiopharmaceutical must be evaluated taking into account each intended use.

§601.31 Definition.

For purposes of this part, diagnostic radiopharmaceutical means:

(a) An article that is intended for use in the diagnosis or monitoring of a disease or a manifestation of a disease in humans and that exhibits spontaneous disintegration of unstable nuclei with the emission of nuclear particles or photons; or

(b) Any nonradioactive reagent kit or nuclide generator that is intended to be used in the preparation of such article as defined in paragraph (a) of this section.
§601.32 General factors relevant to safety and effectiveness.
FDA's determination of the safety and effectiveness of a diagnostic radiopharmaceutical includes consideration of the following:
(a) The proposed use of the diagnostic radiopharmaceutical in the practice of medicine;
(b) The pharmacological and toxicological activity of the diagnostic radiopharmaceutical (including any carrier or ligand component of the diagnostic radiopharmaceutical); and
(c) The estimated absorbed radiation dose of the diagnostic radiopharmaceutical.

§601.33 Indications.
(a) For diagnostic radiopharmaceuticals, the categories of proposed indications for use include, but are not limited to, the following:
   (1) Structure delineation;
   (2) Functional, physiological, or biochemical assessment;
   (3) Disease or pathology detection or assessment; and
   (4) Diagnostic or therapeutic patient management.
(b) Where a diagnostic radiopharmaceutical is not intended to provide disease-specific information, the proposed indications for use may refer to a biochemical, physiological, anatomical, or pathological process or to more than one disease or condition.

§601.34 Evaluation of effectiveness.
(a) The effectiveness of a diagnostic radiopharmaceutical is assessed by evaluating its ability to provide useful clinical information related to its proposed indications for use. The method of this evaluation varies depending upon the proposed indication(s) and may use one or more of the following criteria:
   (1) The claim of structure delineation is established by demonstrating in a defined clinical setting the ability to locate anatomical structures and to characterize their anatomy.
   (2) The claim of functional, physiological, or biochemical assessment is established by demonstrating in a defined clinical setting reliable measurement of function(s) or physiological, biochemical, or molecular process(es).
   (3) The claim of disease or pathology detection or assessment is established by demonstrating in a defined clinical setting that the diagnostic radiopharmaceutical has sufficient accuracy in identifying or characterizing the disease or pathology.
   (4) The claim of diagnostic or therapeutic patient management is established by demonstrating in a defined clinical setting that the test is useful in diagnostic or therapeutic patient management.
   (5) For a claim that does not fall within the indication categories identified in §601.33, the applicant or sponsor should consult FDA on how to establish the effectiveness of the diagnostic radiopharmaceutical for the claim.
(b) The accuracy and usefulness of the diagnostic information is determined by comparison with a reliable assessment of actual clinical status. A reliable assessment of actual clinical status may be provided by a diagnostic standard or standards of
demonstrated accuracy. In the absence of such diagnostic standard(s), the actual clinical status must be established in another manner, e.g., patient followup.

§601.35 Evaluation of safety.

(a) Factors considered in the safety assessment of a diagnostic radiopharmaceutical include, among others, the following:
   (1) The radiation dose;
   (2) The pharmacology and toxicology of the radiopharmaceutical, including any radionuclide, carrier, or ligand;
   (3) The risks of an incorrect diagnostic determination;
   (4) The adverse reaction profile of the drug;
   (5) Results of human experience with the radiopharmaceutical for other uses; and
   (6) Results of any previous human experience with the carrier or ligand of the radiopharmaceutical when the same chemical entity as the carrier or ligand has been used in a previously studied product.

(b) The assessment of the adverse reaction profile includes, but is not limited to, an evaluation of the potential of the diagnostic radiopharmaceutical, including the carrier or ligand, to elicit the following:
   (1) Allergic or hypersensitivity responses,
   (2) Immunologic responses,
   (3) Changes in the physiologic or biochemical function of the target and nontarget tissues, and
   (4) Clinically detectable signs or symptoms.

(c) To establish the safety of a diagnostic radiopharmaceutical, FDA may require, among other information, the following types of data:
   (A) Pharmacology data,
   (B) Toxicology data,
   (C) Clinical adverse event data, and
   (D) Radiation safety assessment.

(2) The amount of new safety data required will depend on the characteristics of the product and available information regarding the safety of the diagnostic radiopharmaceutical, and its carrier or ligand, obtained from other studies and uses. Such information may include, but is not limited to, the dose, route of administration, frequency of use, half-life of the ligand or carrier, half-life of the radionuclide, and results of clinical and preclinical studies. FDA will establish categories of diagnostic radiopharmaceuticals based on defined characteristics relevant to risk and will specify the amount and type of safety data that are appropriate for each category (e.g., required safety data may be limited for diagnostic radiopharmaceuticals with a well established, low-risk profile). Upon reviewing the relevant product characteristics and safety information, FDA will place each diagnostic radiopharmaceutical into the appropriate safety risk category.

(d) Radiation safety assessment. The radiation safety assessment must establish the radiation dose of a diagnostic radiopharmaceutical by radiation dosimetry evaluations.
Subpart E--Accelerated Approval of Biological Products for Serious or Life-Threatening Illnesses

§601.40 Scope.

Source: 57 FR 58959, Dec. 11, 1992, unless otherwise noted.

This subpart applies to certain biological products that have been studied for their safety and effectiveness in treating serious or life-threatening illnesses and that provide meaningful therapeutic benefit to patients over existing treatments (e.g., ability to treat patients unresponsive to, or intolerant of, available therapy, or improved patient response over available therapy).

§601.41 Approval based on a surrogate endpoint or on an effect on a clinical endpoint other than survival or irreversible morbidity.

FDA may grant marketing approval for a biological product on the basis of adequate and well-controlled clinical trials establishing that the biological product has an effect on a surrogate endpoint that is reasonably likely, based on epidemiologic, therapeutic, pathophysiologic, or other evidence, to predict clinical benefit or on the basis of an effect on a clinical endpoint other than survival or irreversible morbidity. Approval under this section will be subject to the requirement that the applicant study the biological product further, to verify and describe its clinical benefit, where there is uncertainty as to the relation of the surrogate endpoint to clinical benefit, or of the observed clinical benefit to ultimate outcome. Postmarketing studies would usually be studies already underway. When required to be conducted, such studies must also be adequate and well-controlled. The applicant shall carry out any such studies with due diligence.

§601.42 Approval with restrictions to assure safe use.

(a) If FDA concludes that a biological product shown to be effective can be safely used only if distribution or use is restricted, FDA will require such postmarketing restrictions as are needed to assure safe use of the biological product, such as:
   (1) Distribution restricted to certain facilities or physicians with special training or experience; or
   (2) Distribution conditioned on the performance of specified medical procedures.

(b) The limitations imposed will be commensurate with the specific safety concerns presented by the biological product.

§601.43 Withdrawal procedures.

(a) For biological products approved under §§601.40 and 601.42, FDA may withdraw approval, following a hearing as provided in part 15 of this chapter, as modified by this section, if:
   (1) A postmarketing clinical study fails to verify clinical benefit;
   (2) The applicant fails to perform the required postmarketing study with due diligence;
(3) Use after marketing demonstrates that postmarketing restrictions are inadequate to ensure safe use of the biological product;
(4) The applicant fails to adhere to the postmarketing restrictions agreed upon;
(5) The promotional materials are false or misleading; or
(6) Other evidence demonstrates that the biological product is not shown to be safe or effective under its conditions of use.

(b) Notice of opportunity for a hearing. The Director of the Center for Biologics Evaluation and Research will give the applicant notice of an opportunity for a hearing on the Center's proposal to withdraw the approval of an application approved under §601.40 or §601.41. The notice, which will ordinarily be a letter, will state generally the reasons for the action and the proposed grounds for the order.

(c) Submission of data and information.
(1) If the applicant fails to file a written request for a hearing within 15 days of receipt of the notice, the applicant waives the opportunity for a hearing.
(2) If the applicant files a timely request for a hearing, the agency will publish a notice of hearing in the Federal Register in accordance with §§12.32(e) and 15.20 of this chapter.
(3) An applicant who requests a hearing under this section must, within 30 days of receipt of the notice of opportunity for a hearing, submit the data and information upon which the applicant intends to rely at the hearing.

(d) Separation of functions. Separation of functions (as specified in §10.55 of this chapter) will not apply at any point in withdrawal proceedings under this section.

(e) Procedures for hearings. Hearings held under this section will be conducted in accordance with the provisions of part 15 of this chapter, with the following modifications:
(1) An advisory committee duly constituted under part 14 of this chapter will be present at the hearing. The committee will be asked to review the issues involved and to provide advice and recommendations to the Commissioner of Food and Drugs.
(2) The presiding officer, the advisory committee members, up to three representatives of the applicant, and up to three representatives of the Center may question any person during or at the conclusion of the person's presentation. No other person attending the hearing may question a person making a presentation. The presiding officer may, as a matter of discretion, permit questions to be submitted to the presiding officer for response by a person making a presentation.

(f) Judicial review. The Commissioner's decision constitutes final agency action from which the applicant may petition for judicial review. Before requesting an order from a court for a stay of action pending review, an applicant must first submit a petition for a stay of action under §10.35 of this chapter.

§601.44 Postmarketing safety reporting.
Biological products approved under this program are subject to the postmarketing recordkeeping and safety reporting applicable to all approved biological products.
§601.45 Promotional materials.
For biological products being considered for approval under this subpart, unless otherwise informed by the agency, applicants must submit to the agency for consideration during the preapproval review period copies of all promotional materials, including promotional labeling as well as advertisements, intended for dissemination or publication within 120 days following marketing approval. After 120 days following marketing approval, unless otherwise informed by the agency, the applicant must submit promotional materials at least 30 days prior to the intended time of initial dissemination of the labeling or initial publication of the advertisement.

§601.46 Termination of requirements.
If FDA determines after approval that the requirements established in §601.42, §601.43, or §601.45 are no longer necessary for the safe and effective use of a biological product, it will so notify the applicant. Ordinarily, for biological products approved under §601.41, these requirements will no longer apply when FDA determines that the required postmarketing study verifies and describes the biological product's clinical benefit and the biological product would be appropriate for approval under traditional procedures. For biological products approved under §601.42, the restrictions would no longer apply when FDA determines that safe use of the biological product can be assured through appropriate labeling. FDA also retains the discretion to remove specific postapproval requirements upon review of a petition submitted by the sponsor in accordance with §10.30.

Subpart F--Confidentiality of Information

§601.50 Confidentiality of data and information in an investigational new drug notice for a biological product.
(a) The existence of an IND notice for a biological product will not be disclosed by the Food and Drug Administration unless it has previously been publicly disclosed or acknowledged.
(b) The availability for public disclosure of all data and information in an IND file for a biological product shall be handled in accordance with the provisions established in §601.51.
(c) Notwithstanding the provisions of §601.51, the Food and Drug Administration shall disclose upon request to an individual on whom an investigational biological product has been used a copy of any adverse reaction report relating to such use.

[39 FR 44656, Dec. 24, 1974]

§601.51 Confidentiality of data and information in applications for biologics licenses.
(a) For purposes of this section the biological product file includes all data and information submitted with or incorporated by reference in any application for a biologics license, IND's incorporated into any such application, master files, and other related submissions. The availability for public disclosure of any record in the
biological product file shall be handled in accordance with the provisions of this section.

(b) The existence of a biological product file will not be disclosed by the Food and Drug Administration before a biologics license application has been approved unless it has previously been publicly disclosed or acknowledged. The Director of the Center for Biologics Evaluation and Research will maintain a list available for public disclosure of biological products for which a license application has been approved.

(c) If the existence of a biological product file has not been publicly disclosed or acknowledged, no data or information in the biological product file is available for public disclosure.

(d) If the existence of a biological product file has been publicly disclosed or acknowledged before a license has been issued, no data or information contained in the file is available for public disclosure before such license is issued, but the Commissioner may, in his discretion, disclose a summary of such selected portions of the safety and effectiveness data as are appropriate for public consideration of a specific pending issue, e.g., at an open session of a Food and Drug Administration advisory committee or pursuant to an exchange of important regulatory information with a foreign government.

(2) Notwithstanding paragraph (d)(1) of this section, FDA will make available to the public upon request the information in the IND that was required to be filed in Docket Number 95S-0158 in the Dockets Management Branch (HFA-305), Food and Drug Administration, 12420 Parklawn Dr., rm. 1-23, Rockville, MD 20857, for investigations involving an exception from informed consent under §50.24 of this chapter. Persons wishing to request this information shall submit a request under the Freedom of Information Act.

(e) After a license has been issued, the following data and information in the biological product file are immediately available for public disclosure unless extraordinary circumstances are shown:

1. All safety and effectiveness data and information.
2. A protocol for a test or study, unless it is shown to fall within the exemption established for trade secrets and confidential commercial or financial information in §20.61 of this chapter.
3. Adverse reaction reports, product experience reports, consumer complaints, and other similar data and information, after deletion of:
   (i) Names and any information that would identify the person using the product.
   (ii) Names and any information that would identify any third party involved with the report, such as a physician or hospital or other institution.
4. A list of all active ingredients and any inactive ingredients previously disclosed to the public, as defined in §20.81 of this chapter.
5. An assay method or other analytical method, unless it serves no regulatory or compliance purpose and it is shown to fall within the exemption established in §20.61 of this chapter.
6. All correspondence and written summaries of oral discussions relating to the biological product file, in accordance with the provisions of part 20 of this chapter.
(7) All records showing the manufacturer's testing of a particular lot, after deletion of
data or information that would show the volume of the drug produced,
manufacturing procedures and controls, yield from raw materials, costs, or other
material falling within §20.61 of this chapter.

(8) All records showing the testing of and action on a particular lot by the Food and
Drug Administration.

(f) The following data and information in a biological product file are not available for
public disclosure unless they have been previously disclosed to the public as defined
in §20.81 of this chapter or they relate to a product or ingredient that has been
abandoned and they no longer represent a trade secret or confidential commercial or
financial information as defined in §20.61 of this chapter:

(1) Manufacturing methods or processes, including quality control procedures.

(2) Production, sales, distribution, and similar data and information, except that any
compilation of such data and information aggregated and prepared in a way that
does not reveal data or information which is not available for public disclosure
under this provision is available for public disclosure.

(3) Quantitative or semiquantitative formulas.

(g) For purposes of this regulation, safety and effectiveness data include all studies and
tests of a biological product on animals and humans and all studies and tests on the
drug for identity, stability, purity, potency, and bioavailability.


Subpart G--Postmarketing Studies

§601.70 Annual progress reports of postmarketing studies.

Source: 65 FR 64618, Oct. 30, 2000, unless otherwise noted.

(a) General requirements. This section applies to all required postmarketing studies (e.g.,
accelerated approval clinical benefit studies, pediatric studies) and postmarketing
studies that an applicant has committed, in writing, to conduct either at the time of
approval of an application or a supplement to an application, or after approval of an
application or a supplement. Postmarketing studies within the meaning of this section
are those that concern:

(1) Clinical safety;

(2) Clinical efficacy;

(3) Clinical pharmacology; and

(4) Nonclinical toxicology.

(b) What to report. Each applicant of a licensed biological product shall submit a report to
FDA on the status of postmarketing studies for each approved product application.
The status of these postmarketing studies shall be reported annually until FDA
notifies the applicant, in writing, that the agency concurs with the applicant's
determination that the study commitment has been fulfilled, or that the study is either
no longer feasible or would no longer provide useful information. Each annual
progress report shall be accompanied by a completed transmittal Form FDA-2252,
and shall include all the information required under this section that the applicant
received or otherwise obtained during the annual reporting interval which ends on the U.S. anniversary date. The report must provide the following information for each postmarketing study:

(1) Applicant's name.
(2) Product name. Include the approved product's proper name and the proprietary name, if any.
(3) Biologics license application (BLA) and supplement number.
(4) Date of U.S. approval of BLA.
(5) Date of postmarketing study commitment.
(6) Description of postmarketing study commitment. The description must include sufficient information to uniquely describe the study. This information may include the purpose of the study, the type of study, the patient population addressed by the study and the indication(s) and dosage(s) that are to be studied.
(7) Schedule for completion and reporting of the postmarketing study commitment. The schedule should include the actual or projected dates for submission of the study protocol to FDA, completion of patient accrual or initiation of an animal study, submission of the final study report to FDA, and any additional milestones or submissions for which projected dates were specified as part of the commitment. In addition, it should include a revised schedule, as appropriate. If the schedule has been previously revised, provide both the original schedule and the most recent, previously submitted revision.
(8) Current status of the postmarketing study commitment. The status of each postmarketing study should be categorized using one of the following terms that describes the study's status on the anniversary date of U.S. approval of the application or other agreed upon date:
   (i) Pending. The study has not been initiated, but does not meet the criterion for delayed.
   (ii) Ongoing. The study is proceeding according to or ahead of the original schedule described under paragraph (b)(7) of this section.
   (iii) Delayed. The study is behind the original schedule described under paragraph (b)(7) of this section.
   (iv) Terminated. The study was ended before completion but a final study report has not been submitted to FDA.
   (v) Submitted. The study has been completed or terminated and a final study report has been submitted to FDA.
(9) Explanation of the study's status. Provide a brief description of the status of the study, including the patient accrual rate (expressed by providing the number of patients or subjects enrolled to date, and the total planned enrollment), and an explanation of the study's status identified under paragraph (b)(8) of this section. If the study has been completed, include the date the study was completed and the date the final study report was submitted to FDA, as applicable. Provide a revised schedule, as well as the reason(s) for the revision, if the schedule under paragraph (b)(7) of this section has changed since the previous report.
(c) When to report. Annual progress reports for postmarketing study commitments entered into by applicants shall be reported to FDA within 60 days of the anniversary date of the U.S. approval of the application for the product.

(d) Where to report. Submit two copies of the annual progress report of postmarketing studies to the Food and Drug Administration, Center for Biologics Evaluations and Research, Document Control Center (HFM-99), 1401 Rockville Pike, Rockville, MD 20852-1448.

(e) Public disclosure of information. Except for the information described in this paragraph, FDA may publicly disclose any information concerning a postmarketing study, within the meaning of this section, if the agency determines that the information is necessary to identify an applicant or to establish the status of the study including the reasons, if any, for failure to conduct, complete, and report the study. Under this section, FDA will not publicly disclose trade secrets, as defined in §20.61 of this chapter, or information, described in §20.63 of this chapter, the disclosure of which would constitute an unwarranted invasion of personal privacy.
Subpart A--General Provisions

§812.1 Scope.
(a) The purpose of this part is to encourage, to the extent consistent with the protection of public health and safety and with ethical standards, the discovery and development of useful devices intended for human use, and to that end to maintain optimum freedom for scientific investigators in their pursuit of this purpose. This part provides procedures for the conduct of clinical investigations of devices. An approved investigational device exemption (IDE) permits a device that otherwise would be required to comply with a performance standard or to have premarket approval to be shipped lawfully for the purpose of conducting investigations of that device. An IDE approved under §812.30 or considered approved under §812.2(b) exempts a device from the requirements of the following sections of the Federal Food, Drug, and Cosmetic Act (the act) and regulations issued thereunder: Misbranding under section 502 of the act, registration, listing, and premarket notification under section 510, performance standards under section 514, premarket approval under section 515, a banned device regulation under section 516, records and reports under section 519, restricted device requirements under section 520(e), good manufacturing practice requirements under section 520(f) except for the requirements found in §820.30, if applicable (unless the sponsor states an intention to comply with these requirements under §812.20(b)(3) or §812.140(b)(4)(v)) and color additive requirements under section 721.

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


§812.2 Applicability.
(a) General. This part applies to all clinical investigations of devices to determine safety and effectiveness, except as provided in paragraph (c) of this section.

(b) Abbreviated requirements. The following categories of investigations are considered to have approved applications for IDE's, unless FDA has notified a sponsor under §812.20(a) that approval of an application is required:

1. An investigation of a device other than a significant risk device, if the device is not a banned device and the sponsor:
   (i) Labels the device in accordance with §812.5;
   (ii) Obtains IRB approval of the investigation after presenting the reviewing IRB with a brief explanation of why the device is not a significant risk device, and maintains such approval;
   (iii) Ensures that each investigator participating in an investigation of the device obtains from each subject under the investigator's care, informed consent
under part 50 and documents it, unless documentation is waived by an IRB under \$56.109\(c\).

(iv) Complies with the requirements of \$812.46 with respect to monitoring investigations;

(v) Maintains the records required under \$812.140\(b\) (4) and (5) and makes the reports required under \$812.150\(b\) (1) through (3) and (5) through (10);

(vi) Ensures that participating investigators maintain the records required by \$812.140\(a\)(3)(i) and make the reports required under \$812.150\(a\) (1), (2), (5), and (7); and

(vii) Complies with the prohibitions in \$812.7 against promotion and other practices.

(2) An investigation of a device other than one subject to paragraph (e) of this section, if the investigation was begun on or before July 16, 1980, and to be completed, and is completed, on or before January 19, 1981.

(c) Exempted investigations. This part, with the exception of \$812.119, does not apply to investigations of the following categories of devices:

(1) A device, other than a transitional device, in commercial distribution immediately before May 28, 1976, when used or investigated in accordance with the indications in labeling in effect at that time.

(2) A device, other than a transitional device, introduced into commercial distribution on or after May 28, 1976, that FDA has determined to be substantially equivalent to a device in commercial distribution immediately before May 28, 1976, and that is used or investigated in accordance with the indications in the labeling FDA reviewed under subpart E of part 807 in determining substantial equivalence.

(3) A diagnostic device, if the sponsor complies with applicable requirements in \$809.10\(c\) and if the testing:

   (i) Is noninvasive,

   (ii) Does not require an invasive sampling procedure that presents significant risk,

   (iii) Does not by design or intention introduce energy into a subject, and

   (iv) Is not used as a diagnostic procedure without confirmation of the diagnosis by another, medically established diagnostic product or procedure.

(4) A device undergoing consumer preference testing, testing of a modification, or testing of a combination of two or more devices in commercial distribution, if the testing is not for the purpose of determining safety or effectiveness and does not put subjects at risk.

(5) A device intended solely for veterinary use.

(6) A device shipped solely for research on or with laboratory animals and labeled in accordance with \$812.5\(c\).

(7) A custom device as defined in \$812.3\(b\), unless the device is being used to determine safety or effectiveness for commercial distribution.

(d) Limit on certain exemptions. In the case of class II or class III device described in paragraph (c)(1) or (2) of this section, this part applies beginning on the date stipulated in an FDA regulation or order that calls for the submission of premarket
approval applications for an unapproved class III device, or establishes a performance standard for a class II device.

(e) Investigations subject to IND's. A sponsor that, on July 16, 1980, has an effective investigational new drug application (IND) for an investigation of a device shall continue to comply with the requirements of part 312 until 90 days after that date. To continue the investigation after that date, a sponsor shall comply with paragraph (b)(1) of this section, if the device is not a significant risk device, or shall have obtained FDA approval under §812.30 of an IDE application for the investigation of the device.


§812.3 Definitions.

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

(b) Custom device means a device that:

(1) Necessarily deviates from devices generally available or from an applicable performance standard or premarket approval requirement in order to comply with the order of an individual physician or dentist;

(2) Is not generally available to, or generally used by, other physicians or dentists;

(3) Is not generally available in finished form for purchase or for dispensing upon prescription;

(4) Is not offered for commercial distribution through labeling or advertising; and

(5) Is intended for use by an individual patient named in the order of a physician or dentist, and is to be made in a specific form for that patient, or is intended to meet the special needs of the physician or dentist in the course of professional practice.

(c) FDA means the Food and Drug Administration.

(d) Implant means a device that is placed into a surgically or naturally formed cavity of the human body if it is intended to remain there for a period of 30 days or more. FDA may, in order to protect public health, determine that devices placed in subjects for shorter periods are also “implants” for purposes of this part.

(e) Institution means a person, other than an individual, who engages in the conduct of research on subjects or in the delivery of medical services to individuals as a primary activity or as an adjunct to providing residential or custodial care to humans. The term includes, for example, a hospital, retirement home, confinement facility, academic establishment, and device manufacturer. The term has the same meaning as “facility” in section 520(g) of the act.

(f) Institutional review board (IRB) means any board, committee, or other group formally designated by an institution to review biomedical research involving subjects and established, operated, and functioning in conformance with part 56. The term has the same meaning as “institutional review committee” in section 520(g) of the act.

(g) Investigational device means a device, including a transitional device, that is the object of an investigation.

(h) Investigation means a clinical investigation or research involving one or more subjects to determine the safety or effectiveness of a device.
(i) **Investigator** means an individual who actually conducts a clinical investigation, i.e., under whose immediate direction the test article is administered or dispensed to, or used involving, a subject, or, in the event of an investigation conducted by a team of individuals, is the responsible leader of that team.

(j) **Monitor**, when used as a noun, means an individual designated by a sponsor or contract research organization to oversee the progress of an investigation. The monitor may be an employee of a sponsor or a consultant to the sponsor, or an employee of or consultant to a contract research organization. **Monitor**, when used as a verb, means to oversee an investigation.

(k) **Noninvasive**, when applied to a diagnostic device or procedure, means one that does not by design or intention:

1. Penetrate or pierce the skin or mucous membranes of the body, the ocular cavity, or the urethra, or
2. enter the ear beyond the external auditory canal, the nose beyond the nares, the mouth beyond the pharynx, the anal canal beyond the rectum, or the vagina beyond the cervical os. For purposes of this part, blood sampling that involves simple venipuncture is considered noninvasive, and the use of surplus samples of body fluids or tissues that are left over from samples taken for noninvestigational purposes is also considered noninvasive.

(l) **Person** includes any individual, partnership, corporation, association, scientific or academic establishment, Government agency or organizational unit of a Government agency, and any other legal entity.

(m) **Significant risk device** means an investigational device that:

1. Is intended as an implant and presents a potential for serious risk to the health, safety, or welfare of a subject;
2. Is purported or represented to be for a use in supporting or sustaining human life and presents a potential for serious risk to the health, safety, or welfare of a subject;
3. Is for a use of substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise preventing impairment of human health and presents a potential for serious risk to the health, safety, or welfare of a subject; or
4. Otherwise presents a potential for serious risk to the health, safety, or welfare of a subject.

(n) **Sponsor** means a person who initiates, but who does not actually conduct, the investigation, that is, the investigational device is administered, dispensed, or used under the immediate direction of another individual. A person other than an individual that uses one or more of its own employees to conduct an investigation that it has initiated is a sponsor, not a sponsor-investigator, and the employees are investigators.

(o) **Sponsor-investigator** means an individual who both initiates and actually conducts, alone or with others, an investigation, that is, under whose immediate direction the investigational device is administered, dispensed, or used. The term does not include any person other than an individual. The obligations of a sponsor-investigator under this part include those of an investigator and those of a sponsor.
(p) **Subject** means a human who participates in an investigation, either as an individual on whom or on whose specimen an investigational device is used or as a control. A subject may be in normal health or may have a medical condition or disease.

(q) **Termination** means a discontinuance, by sponsor or by withdrawal of IRB or FDA approval, of an investigation before completion.

(r) **Transitional device** means a device subject to section 520(l) of the act, that is, a device that FDA considered to be a new drug or an antibiotic drug before May 28, 1976.

(s) **Unanticipated adverse device effect** means any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.


**§812.5 Labeling of investigational devices.**

(a) **Contents.** An investigational device or its immediate package shall bear a label with the following information: the name and place of business of the manufacturer, packer, or distributor (in accordance with §801.1), the quantity of contents, if appropriate, and the following statement: “CAUTION--Investigational device. Limited by Federal (or United States) law to investigational use.” The label or other labeling shall describe all relevant contraindications, hazards, adverse effects, interfering substances or devices, warnings, and precautions.

(b) **Prohibitions.** The labeling of an investigational device shall not bear any statement that is false or misleading in any particular and shall not represent that the device is safe or effective for the purposes for which it is being investigated.

(c) **Animal research.** An investigational device shipped solely for research on or with laboratory animals shall bear on its label the following statement: “CAUTION--Device for investigational use in laboratory animals or other tests that do not involve human subjects.”


**§812.7 Prohibition of promotion and other practices.**

A sponsor, investigator, or any person acting for or on behalf of a sponsor or investigator shall not:

(a) Promote or test market an investigational device, until after FDA has approved the device for commercial distribution.

(b) Commercialize an investigational device by charging the subjects or investigators for a device a price larger than that necessary to recover costs of manufacture, research, development, and handling.

(c) Unduly prolong an investigation. If data developed by the investigation indicate in the case of a class III device that premarket approval cannot be justified or in the case of a class II device that it will not comply with an applicable performance standard or an amendment to that standard, the sponsor shall promptly terminate the investigation.
(d) Represent that an investigational device is safe or effective for the purposes for which it is being investigated.

§812.10 Waivers.
(a) Request. A sponsor may request FDA to waive any requirement of this part. A waiver request, with supporting documentation, may be submitted separately or as part of an application to the address in §812.19.
(b) FDA action. FDA may by letter grant a waiver of any requirement that FDA finds is not required by the act and is unnecessary to protect the rights, safety, or welfare of human subjects.
(c) Effect of request. Any requirement shall continue to apply unless and until FDA waives it.

§812.18 Import and export requirements.
(a) Imports. In addition to complying with other requirements of this part, a person who imports or offers for importation an investigational device subject to this part shall be the agent of the foreign exporter with respect to investigations of the device and shall act as the sponsor of the clinical investigation, or ensure that another person acts as the agent of the foreign exporter and the sponsor of the investigation.
(b) Exports. A person exporting an investigational device subject to this part shall obtain FDA's prior approval, as required by section 801(e) of the act or comply with section 802 of the act.


§812.19 Address for IDE correspondence.
If you are sending an application, supplemental application, report, request for waiver, request for import or export approval, or other correspondence relating to matters covered by this part, you must address it to the Center for Devices and Radiological Health, Document Mail Center (HFZ-401), Food and Drug Administration, 9200 Corporate Blvd., Rockville, MD 20850. You must state on the outside wrapper of each submission what the submission is, for example, an “IDE application,” a “supplemental IDE application,” or a “correspondence concerning an IDE (or an IDE application).”

[65 FR 17137, Mar. 31, 2000]

Subpart B--Application and Administrative Action

§812.20 Application.
(a) Submission.
(1) A sponsor shall submit an application to FDA if the sponsor intends to use a significant risk device in an investigation, intends to conduct an investigation that involves an exception from informed consent under §50.24 of this chapter, or if FDA notifies the sponsor that an application is required for an investigation.
(2) A sponsor shall not begin an investigation for which FDA's approval of an application is required until FDA has approved the application.

(3) A sponsor shall submit three copies of a signed “Application for an Investigational Device Exemption” (IDE application), together with accompanying materials, by registered mail or by hand to the address in §812.19. Subsequent correspondence concerning an application or a supplemental application shall be submitted by registered mail or by hand.

(4)(i) A sponsor shall submit a separate IDE for any clinical investigation involving an exception from informed consent under §50.24 of this chapter. Such a clinical investigation is not permitted to proceed without the prior written authorization of FDA. FDA shall provide a written determination 30 days after FDA receives the IDE or earlier.

(ii) If the investigation involves an exception from informed consent under §50.24 of this chapter, the sponsor shall prominently identify on the cover sheet that the investigation is subject to the requirements in §50.24 of this chapter.

(b) Contents. An IDE application shall include, in the following order:

(1) The name and address of the sponsor.

(2) A complete report of prior investigations of the device and an accurate summary of those sections of the investigational plan described in §812.25(a) through (e) or, in lieu of the summary, the complete plan. The sponsor shall submit to FDA a complete investigational plan and a complete report of prior investigations of the device if no IRB has reviewed them, if FDA has found an IRB's review inadequate, or if FDA requests them.

(3) A description of the methods, facilities, and controls used for the manufacture, processing, packing, storage, and, where appropriate, installation of the device, in sufficient detail so that a person generally familiar with good manufacturing practices can make a knowledgeable judgment about the quality control used in the manufacture of the device.

(4) An example of the agreements to be entered into by all investigators to comply with investigator obligations under this part, and a list of the names and addresses of all investigators who have signed the agreement.

(5) A certification that all investigators who will participate in the investigation have signed the agreement, that the list of investigators includes all the investigators participating in the investigation, and that no investigators will be added to the investigation until they have signed the agreement.

(6) A list of the name, address, and chairperson of each IRB that has been or will be asked to review the investigation and a certification of the action concerning the investigation taken by each such IRB.

(7) The name and address of any institution at which a part of the investigation may be conducted that has not been identified in accordance with paragraph (b)(6) of this section.

(8) If the device is to be sold, the amount to be charged and an explanation of why sale does not constitute commercialization of the device.

(9) A claim for categorical exclusion under §25.30 or 25.34 or an environmental assessment under §25.40.
(10) Copies of all labeling for the device.
(11) Copies of all forms and informational materials to be provided to subjects to obtain informed consent.
(12) Any other relevant information FDA requests for review of the application.
(c) Additional information. FDA may request additional information concerning an investigation or revision in the investigational plan. The sponsor may treat such a request as a disapproval of the application for purposes of requesting a hearing under part 16.
(d) Information previously submitted. Information previously submitted to the Center for Devices and Radiological Health in accordance with this chapter ordinarily need not be resubmitted, but may be incorporated by reference.


§812.25 Investigational plan.
The investigational plan shall include, in the following order:
(a) Purpose. The name and intended use of the device and the objectives and duration of the investigation.
(b) Protocol. A written protocol describing the methodology to be used and an analysis of the protocol demonstrating that the investigation is scientifically sound.
(c) Risk analysis. A description and analysis of all increased risks to which subjects will be exposed by the investigation; the manner in which these risks will be minimized; a justification for the investigation; and a description of the patient population, including the number, age, sex, and condition.
(d) Description of device. A description of each important component, ingredient, property, and principle of operation of the device and of each anticipated change in the device during the course of the investigation.
(e) Monitoring procedures. The sponsor's written procedures for monitoring the investigation and the name and address of any monitor.
(f) Labeling. Copies of all labeling for the device.
(g) Consent materials. Copies of all forms and informational materials to be provided to subjects to obtain informed consent.
(h) IRB information. A list of the names, locations, and chairpersons of all IRB's that have been or will be asked to review the investigation, and a certification of any action taken by any of those IRB's with respect to the investigation.
(i) Other institutions. The name and address of each institution at which a part of the investigation may be conducted that has not been identified in paragraph (h) of this section.
(j) Additional records and reports. A description of records and reports that will be maintained on the investigation in addition to those prescribed in subpart G.

§812.27 Report of prior investigations.
(a) General. The report of prior investigations shall include reports of all prior clinical, animal, and laboratory testing of the device and shall be comprehensive and adequate to justify the proposed investigation.
(b) Specific contents. The report also shall include:
(1) A bibliography of all publications, whether adverse or supportive, that are relevant to an evaluation of the safety or effectiveness of the device, copies of all published and unpublished adverse information, and, if requested by an IRB or FDA, copies of other significant publications.

(2) A summary of all other unpublished information (whether adverse or supportive) in the possession of, or reasonably obtainable by, the sponsor that is relevant to an evaluation of the safety or effectiveness of the device.

(3) If information on nonclinical laboratory studies is provided, a statement that all such studies have been conducted in compliance with applicable requirements in the good laboratory practice regulations in part 58, or if any such study was not conducted in compliance with such regulations, a brief statement of the reason for the noncompliance. Failure or inability to comply with this requirement does not justify failure to provide information on a relevant nonclinical test study.


§812.30 FDA action on applications.

(a) Approval or disapproval. FDA will notify the sponsor in writing of the date it receives an application. FDA may approve an investigation as proposed, approve it with modifications, or disapprove it. An investigation may not begin until:

(1) Thirty days after FDA receives the application at the address in §812.19 for the investigation of a device other than a banned device, unless FDA notifies the sponsor that the investigation may not begin; or

(2) FDA approves, by order, an IDE for the investigation.

(b) Grounds for disapproval or withdrawal. FDA may disapprove or withdraw approval of an application if FDA finds that:

(1) There has been a failure to comply with any requirement of this part or the act, any other applicable regulation or statute, or any condition of approval imposed by an IRB or FDA.

(2) The application or a report contains an untrue statement of a material fact, or omits material information required by this part.

(3) The sponsor fails to respond to a request for additional information within the time prescribed by FDA.

(4) There is reason to believe that the risks to the subjects are not outweighed by the anticipated benefits to the subjects and the importance of the knowledge to be gained, or informed consent is inadequate, or the investigation is scientifically unsound, or there is reason to believe that the device as used is ineffective.

(5) It is otherwise unreasonable to begin or to continue the investigation owing to the way in which the device is used or the inadequacy of:

(i) The report of prior investigations or the investigational plan;

(ii) The methods, facilities, and controls used for the manufacturing, processing, packaging, storage, and, where appropriate, installation of the device; or

(iii) Monitoring and review of the investigation.

(c) Notice of disapproval or withdrawal. If FDA disapproves an application or proposes to withdraw approval of an application, FDA will notify the sponsor in writing.
(1) A disapproval order will contain a complete statement of the reasons for disapproval and a statement that the sponsor has an opportunity to request a hearing under part 16.

(2) A notice of a proposed withdrawal of approval will contain a complete statement of the reasons for withdrawal and a statement that the sponsor has an opportunity to request a hearing under part 16. FDA will provide the opportunity for hearing before withdrawal of approval, unless FDA determines in the notice that continuation of testing under the exemption will result in an unreasonable risk to the public health and orders withdrawal of approval before any hearing.


§812.35 Supplemental applications.

(a) Changes in investigational plan—

(1) Changes requiring prior approval. Except as described in paragraphs (a)(2) through (a)(4) of this section, a sponsor must obtain approval of a supplemental application under §812.30(a), and IRB approval when appropriate (see §§56.110 and 56.111 of this chapter), prior to implementing a change to an investigational plan. If a sponsor intends to conduct an investigation that involves an exception to informed consent under §50.24 of this chapter, the sponsor shall submit a separate investigational device exemption (IDE) application in accordance with §812.20(a).

(2) Changes effected for emergency use. The requirements of paragraph (a)(1) of this section regarding FDA approval of a supplement do not apply in the case of a deviation from the investigational plan to protect the life or physical well-being of a subject in an emergency. Such deviation shall be reported to FDA within 5-working days after the sponsor learns of it (see §812.150(a)(4)).

(3) Changes effected with notice to FDA within 5 days. A sponsor may make certain changes without prior approval of a supplemental application under paragraph (a)(1) of this section if the sponsor determines that these changes meet the criteria described in paragraphs (a)(3)(i) and (a)(3)(ii) of this section, on the basis of credible information defined in paragraph (a)(3)(iii) of this section, and the sponsor provides notice to FDA within 5-working days of making these changes.

(i) Developmental changes. The requirements in paragraph (a)(1) of this section regarding FDA approval of a supplement do not apply to developmental changes in the device (including manufacturing changes) that do not constitute a significant change in design or basic principles of operation and that are made in response to information gathered during the course of an investigation.

(ii) Changes to clinical protocol. The requirements in paragraph (a)(1) of this section regarding FDA approval of a supplement do not apply to changes to clinical protocols that do not affect:

(A) The validity of the data or information resulting from the completion of the approved protocol, or the relationship of likely patient risk to benefit relied upon to approve the protocol;
(B) The scientific soundness of the investigational plan; or
(C) The rights, safety, or welfare of the human subjects involved in the investigation.

(iii) Definition of credible information. (A) Credible information to support developmental changes in the device (including manufacturing changes) includes data generated under the design control procedures of §820.30, preclinical/animal testing, peer reviewed published literature, or other reliable information such as clinical information gathered during a trial or marketing.

(B) Credible information to support changes to clinical protocols is defined as the sponsor's documentation supporting the conclusion that a change does not have a significant impact on the study design or planned statistical analysis, and that the change does not affect the rights, safety, or welfare of the subjects. Documentation shall include information such as peer reviewed published literature, the recommendation of the clinical investigator(s), and/or the data gathered during the clinical trial or marketing.

(iv) Notice of IDE change. Changes meeting the criteria in paragraphs (a)(3)(i) and (a)(3)(ii) of this section that are supported by credible information as defined in paragraph (a)(3)(iii) of this section may be made without prior FDA approval if the sponsor submits a notice of the change to the IDE not later than 5-working days after making the change. Changes to devices are deemed to occur on the date the device, manufactured incorporating the design or manufacturing change, is distributed to the investigator(s). Changes to a clinical protocol are deemed to occur when a clinical investigator is notified by the sponsor that the change should be implemented in the protocol or, for sponsor-investigator studies, when a sponsor-investigator incorporates the change in the protocol. Such notices shall be identified as a “notice of IDE change.”

(A) For a developmental or manufacturing change to the device, the notice shall include a summary of the relevant information gathered during the course of the investigation upon which the change was based; a description of the change to the device or manufacturing process (cross-referenced to the appropriate sections of the original device description or manufacturing process); and, if design controls were used to assess the change, a statement that no new risks were identified by appropriate risk analysis and that the verification and validation testing, as appropriate, demonstrated that the design outputs met the design input requirements. If another method of assessment was used, the notice shall include a summary of the information which served as the credible information supporting the change.

(B) For a protocol change, the notice shall include a description of the change (cross-referenced to the appropriate sections of the original protocol); an assessment supporting the conclusion that the change does not have a significant impact on the study design or planned statistical analysis; and a summary of the information that served as
the credible information supporting the sponsor's determination that
the change does not affect the rights, safety, or welfare of the subjects.

(4) Changes submitted in annual report. The requirements of paragraph (a)(1) of this
section do not apply to minor changes to the purpose of the study, risk analysis,
monitoring procedures, labeling, informed consent materials, and IRB
information that do not affect:

(i) The validity of the data or information resulting from the completion of the
approved protocol, or the relationship of likely patient risk to benefit relied
upon to approve the protocol;

(ii) The scientific soundness of the investigational plan; or

(iii) The rights, safety, or welfare of the human subjects involved in the
investigation. Such changes shall be reported in the annual progress report
for the IDE, under §812.150(b)(5).

(b) IRB approval for new facilities. A sponsor shall submit to FDA a certification of any
IRB approval of an investigation or a part of an investigation not included in the IDE
application. If the investigation is otherwise unchanged, the supplemental application
shall consist of an updating of the information required by §812.20(b) and (c) and a
description of any modifications in the investigational plan required by the IRB as a
condition of approval. A certification of IRB approval need not be included in the
initial submission of the supplemental application, and such certification is not a
precondition for agency consideration of the application. Nevertheless, a sponsor may
not begin a part of an investigation at a facility until the IRB has approved the
investigation, FDA has received the certification of IRB approval, and FDA, under
§812.30(a), has approved the supplemental application relating to that part of the
investigation (see §56.103(a)).

FR 64625, Nov. 23, 1998]

§812.36 Treatment use of an investigational device.

(a) General. A device that is not approved for marketing may be under clinical
investigation for a serious or immediately life-threatening disease or condition in
patients for whom no comparable or satisfactory alternative device or other therapy is
available. During the clinical trial or prior to final action on the marketing
application, it may be appropriate to use the device in the treatment of patients not in
the trial under the provisions of a treatment investigational device exemption (IDE).
The purpose of this section is to facilitate the availability of promising new devices to
desperately ill patients as early in the device development process as possible, before
general marketing begins, and to obtain additional data on the device's safety and
effectiveness. In the case of a serious disease, a device ordinarily may be made
available for treatment use under this section after all clinical trials have been
completed. In the case of an immediately life-threatening disease, a device may be
made available for treatment use under this section prior to the completion of all
clinical trials. For the purpose of this section, an “immediately life-threatening”
disease means a stage of a disease in which there is a reasonable likelihood that death
will occur within a matter of months or in which premature death is likely without
early treatment. For purposes of this section, “treatment use” of a device includes the use of a device for diagnostic purposes.

(b) Criteria. FDA shall consider the use of an investigational device under a treatment IDE if:

(1) The device is intended to treat or diagnose a serious or immediately life-threatening disease or condition;
(2) There is no comparable or satisfactory alternative device or other therapy available to treat or diagnose that stage of the disease or condition in the intended patient population;
(3) The device is under investigation in a controlled clinical trial for the same use under an approved IDE, or such clinical trials have been completed; and
(4) The sponsor of the investigation is actively pursuing marketing approval/clearance of the investigational device with due diligence.

(c) Applications for treatment use.

(1) A treatment IDE application shall include, in the following order:

(i) The name, address, and telephone number of the sponsor of the treatment IDE;
(ii) The intended use of the device, the criteria for patient selection, and a written protocol describing the treatment use;
(iii) An explanation of the rationale for use of the device, including, as appropriate, either a list of the available regimens that ordinarily should be tried before using the investigational device or an explanation of why the use of the investigational device is preferable to the use of available marketed treatments;
(iv) A description of clinical procedures, laboratory tests, or other measures that will be used to evaluate the effects of the device and to minimize risk;
(v) Written procedures for monitoring the treatment use and the name and address of the monitor;
(vi) Instructions for use for the device and all other labeling as required under §812.5(a) and (b);
(vii) Information that is relevant to the safety and effectiveness of the device for the intended treatment use. Information from other IDE's may be incorporated by reference to support the treatment use;
(viii) A statement of the sponsor's commitment to meet all applicable responsibilities under this part and part 56 of this chapter and to ensure compliance of all participating investigators with the informed consent requirements of part 50 of this chapter;
(ix) An example of the agreement to be signed by all investigators participating in the treatment IDE and certification that no investigator will be added to the treatment IDE before the agreement is signed; and
(x) If the device is to be sold, the price to be charged and a statement indicating that the price is based on manufacturing and handling costs only.

(2) A licensed practitioner who receives an investigational device for treatment use under a treatment IDE is an “investigator” under the IDE and is responsible for meeting all applicable investigator responsibilities under this part and parts 50 and 56 of this chapter.
(d) FDA action on treatment IDE applications.

(1) Approval of treatment IDE's. Treatment use may begin 30 days after FDA receives the treatment IDE submission at the address specified in §812.19, unless FDA notifies the sponsor in writing earlier than the 30 days that the treatment use may or may not begin. FDA may approve the treatment use as proposed or approve it with modifications.

(2) Disapproval or withdrawal of approval of treatment IDE's. FDA may disapprove or withdraw approval of a treatment IDE if:

(i) The criteria specified in §812.36(b) are not met or the treatment IDE does not contain the information required in §812.36(c);
(ii) FDA determines that any of the grounds for disapproval or withdrawal of approval listed in §812.30(b)(1) through (b)(5) apply;
(iii) The device is intended for a serious disease or condition and there is insufficient evidence of safety and effectiveness to support such use;
(iv) The device is intended for an immediately life-threatening disease or condition and the available scientific evidence, taken as a whole, fails to provide a reasonable basis for concluding that the device:
(A) May be effective for its intended use in its intended population; or
(B) Would not expose the patients to whom the device is to be administered to an unreasonable and significant additional risk of illness or injury;
(v) There is reasonable evidence that the treatment use is impeding enrollment in, or otherwise interfering with the conduct or completion of, a controlled investigation of the same or another investigational device;
(vi) The device has received marketing approval/clearance or a comparable device or therapy becomes available to treat or diagnose the same indication in the same patient population for which the investigational device is being used;
(vii) The sponsor of the controlled clinical trial is not pursuing marketing approval/clearance with due diligence;
(viii) Approval of the IDE for the controlled clinical investigation of the device has been withdrawn; or
(ix) The clinical investigator(s) named in the treatment IDE are not qualified by reason of their scientific training and/or experience to use the investigational device for the intended treatment use.

(3) Notice of disapproval or withdrawal. If FDA disapproves or proposes to withdraw approval of a treatment IDE, FDA will follow the procedures set forth in §812.30(c).

(e) Safeguards. Treatment use of an investigational device is conditioned upon the sponsor and investigators complying with the safeguards of the IDE process and the regulations governing informed consent (part 50 of this chapter) and institutional review boards (part 56 of this chapter).

(f) Reporting requirements. The sponsor of a treatment IDE shall submit progress reports on a semi-annual basis to all reviewing IRB's and FDA until the filing of a marketing application. These reports shall be based on the period of time since initial approval of the treatment IDE and shall include the number of patients treated with the device.
under the treatment IDE, the names of the investigators participating in the treatment IDE, and a brief description of the sponsor's efforts to pursue marketing approval/clearance of the device. Upon filing of a marketing application, progress reports shall be submitted annually in accordance with §812.150(b)(5). The sponsor of a treatment IDE is responsible for submitting all other reports required under §812.150.


§812.38 Confidentiality of data and information.

(a) Existence of IDE. FDA will not disclose the existence of an IDE unless its existence has previously been publicly disclosed or acknowledged, until FDA approves an application for premarket approval of the device subject to the IDE; or a notice of completion of a product development protocol for the device has become effective.

(b) Availability of summaries or data.

(1) FDA will make publicly available, upon request, a detailed summary of information concerning the safety and effectiveness of the device that was the basis for an order approving, disapproving, or withdrawing approval of an application for an IDE for a banned device. The summary shall include information on any adverse effect on health caused by the device.

(2) If a device is a banned device or if the existence of an IDE has been publicly disclosed or acknowledged, data or information contained in the file is not available for public disclosure before approval of an application for premarket approval or the effective date of a notice of completion of a product development protocol except as provided in this section. FDA may, in its discretion, disclose a summary of selected portions of the safety and effectiveness data, that is, clinical, animal, or laboratory studies and tests of the device, for public consideration of a specific pending issue.

(3) If the existence of an IDE file has not been publicly disclosed or acknowledged, no data or information in the file are available for public disclosure except as provided in paragraphs (b)(1) and (c) of this section.

(4) Notwithstanding paragraph (b)(2) of this section, FDA will make available to the public, upon request, the information in the IDE that was required to be filed in Docket Number 95S-0158 in the Dockets Management Branch (HFA-305), Food and Drug Administration, 12420 Parklawn Dr., rm. 1-23, Rockville, MD 20857, for investigations involving an exception from informed consent under §50.24 of this chapter. Persons wishing to request this information shall submit a request under the Freedom of Information Act.

(c) Reports of adverse effects. Upon request or on its own initiative, FDA shall disclose to an individual on whom an investigational device has been used a copy of a report of adverse device effects relating to that use.

(d) Other rules. Except as otherwise provided in this section, the availability for public disclosure of data and information in an IDE file shall be handled in accordance with §814.9.

Subpart C--Responsibilities of Sponsors

§812.40 General responsibilities of sponsors.
Sponsors are responsible for selecting qualified investigators and providing them with the information they need to conduct the investigation properly, ensuring proper monitoring of the investigation, ensuring that IRB review and approval are obtained, submitting an IDE application to FDA, and ensuring that any reviewing IRB and FDA are promptly informed of significant new information about an investigation. Additional responsibilities of sponsors are described in subparts B and G.

§812.42 FDA and IRB approval.
A sponsor shall not begin an investigation or part of an investigation until an IRB and FDA have both approved the application or supplemental application relating to the investigation or part of an investigation.

[46 FR 8957, Jan. 27, 1981]

§812.43 Selecting investigators and monitors.
(a) Selecting investigators. A sponsor shall select investigators qualified by training and experience to investigate the device.
(b) Control of device. A sponsor shall ship investigational devices only to qualified investigators participating in the investigation.
(c) Obtaining agreements. A sponsor shall obtain from each participating investigator a signed agreement that includes:
   (1) The investigator's curriculum vitae.
   (2) Where applicable, a statement of the investigator's relevant experience, including the dates, location, extent, and type of experience.
   (3) If the investigator was involved in an investigation or other research that was terminated, an explanation of the circumstances that led to termination.
   (4) A statement of the investigator's commitment to:
      (i) Conduct the investigation in accordance with the agreement, the investigational plan, this part and other applicable FDA regulations, and conditions of approval imposed by the reviewing IRB or FDA;
      (ii) Supervise all testing of the device involving human subjects; and
      (iii) Ensure that the requirements for obtaining informed consent are met.
   (5) Sufficient accurate financial disclosure information to allow the sponsor to submit a complete and accurate certification or disclosure statement as required under part 54 of this chapter. The sponsor shall obtain a commitment from the clinical investigator to promptly update this information if any relevant changes occur during the course of the investigation and for 1 year following completion of the study. This information shall not be submitted in an investigational device exemption application, but shall be submitted in any marketing application involving the device.
(d) Selecting monitors. A sponsor shall select monitors qualified by training and experience to monitor the investigational study in accordance with this part and other applicable FDA regulations.
§812.45 Informing investigators.
A sponsor shall supply all investigators participating in the investigation with copies of
the investigational plan and the report of prior investigations of the device.

§812.46 Monitoring investigations.
(a) Securing compliance. A sponsor who discovers that an investigator is not complying
with the signed agreement, the investigational plan, the requirements of this part or
other applicable FDA regulations, or any conditions of approval imposed by the
reviewing IRB or FDA shall promptly either secure compliance, or discontinue
shipments of the device to the investigator and terminate the investigator's
participation in the investigation. A sponsor shall also require such an investigator to
dispose of or return the device, unless this action would jeopardize the rights, safety,
or welfare of a subject.

(b) Unanticipated adverse device effects.
(1) A sponsor shall immediately conduct an evaluation of any unanticipated adverse
device effect.

(2) A sponsor who determines that an unanticipated adverse device effect presents an
unreasonable risk to subjects shall terminate all investigations or parts of
investigations presenting that risk as soon as possible. Termination shall occur
not later than 5 working days after the sponsor makes this determination and not
later than 15 working days after the sponsor first received notice of the effect.

(c) Resumption of terminated studies. If the device is a significant risk device, a sponsor
may not resume a terminated investigation without IRB and FDA approval. If the
device is not a significant risk device, a sponsor may not resume a terminated
investigation without IRB approval and, if the investigation was terminated under
paragraph (b)(2) of this section, FDA approval.

§812.47 Emergency research under §50.24 of this chapter.
(a) The sponsor shall monitor the progress of all investigations involving an exception
from informed consent under §50.24 of this chapter. When the sponsor receives from
the IRB information concerning the public disclosures under §50.24(a)(7)(ii) and
(a)(7)(iii) of this chapter, the sponsor shall promptly submit to the IDE file and to
Docket Number 95S-0158 in the Dockets Management Branch (HFA-305), Food and
Drug Administration, 12420 Parklawn Dr., rm. 1-23, Rockville, MD 20857, copies of
the information that was disclosed, identified by the IDE number.

(b) The sponsor also shall monitor such investigations to determine when an IRB
determines that it cannot approve the research because it does not meet the criteria in
the exception in §50.24(a) of this chapter or because of other relevant ethical
corns. The sponsor promptly shall provide this information in writing to FDA,
investigators who are asked to participate in this or a substantially equivalent clinical
investigation, and other IRB's that are asked to review this or a substantially
equivalent investigation.

Subpart D--IRB Review and Approval

§812.60 IRB composition, duties, and functions.
An IRB reviewing and approving investigations under this part shall comply with the requirements of part 56 in all respects, including its composition, duties, and functions.
[46 FR 8957, Jan. 27, 1981]

§812.62 IRB approval.
(a) An IRB shall review and have authority to approve, require modifications in (to secure approval), or disapprove all investigations covered by this part.
(b) If no IRB exists or if FDA finds that an IRB's review is inadequate, a sponsor may submit an application to FDA.
[46 FR 8957, Jan. 27, 1981]

§812.64 IRB's continuing review.
The IRB shall conduct its continuing review of an investigation in accordance with part 56.
[46 FR 8957, Jan. 27, 1981]

§812.66 Significant risk device determinations.
If an IRB determines that an investigation, presented for approval under §812.2(b)(1)(ii), involves a significant risk device, it shall so notify the investigator and, where appropriate, the sponsor. A sponsor may not begin the investigation except as provided in §812.30(a).
[46 FR 8957, Jan. 27, 1981]

Subpart E--Responsibilities of Investigators

§812.100 General responsibilities of investigators.
An investigator is responsible for ensuring that an investigation is conducted according to the signed agreement, the investigational plan and applicable FDA regulations, for protecting the rights, safety, and welfare of subjects under the investigator's care, and for the control of devices under investigation. An investigator also is responsible for ensuring that informed consent is obtained in accordance with part 50 of this chapter. Additional responsibilities of investigators are described in subpart G.

§812.110 Specific responsibilities of investigators.
(a) Awaiting approval. An investigator may determine whether potential subjects would be interested in participating in an investigation, but shall not request the written
informed consent of any subject to participate, and shall not allow any subject to participate before obtaining IRB and FDA approval.

(b) Compliance. An investigator shall conduct an investigation in accordance with the signed agreement with the sponsor, the investigational plan, this part and other applicable FDA regulations, and any conditions of approval imposed by an IRB or FDA.

c) Supervising device use. An investigator shall permit an investigational device to be used only with subjects under the investigator's supervision. An investigator shall not supply an investigational device to any person not authorized under this part to receive it.

d) Financial disclosure. A clinical investigator shall disclose to the sponsor sufficient accurate financial information to allow the applicant to submit complete and accurate certification or disclosure statements required under part 54 of this chapter. The investigator shall promptly update this information if any relevant changes occur during the course of the investigation and for 1 year following completion of the study.

e) Disposing of device. Upon completion or termination of a clinical investigation or the investigator's part of an investigation, or at the sponsor's request, an investigator shall return to the sponsor any remaining supply of the device or otherwise dispose of the device as the sponsor directs.


§812.119 Disqualification of a clinical investigator.

(a) If FDA has information indicating that an investigator has repeatedly or deliberately failed to comply with the requirements of this part, part 50, or part 56 of this chapter, or has repeatedly or deliberately submitted false information either to the sponsor of the investigation or in any required report, the Center for Devices and Radiological Health will furnish the investigator written notice of the matter under complaint and offer the investigator an opportunity to explain the matter in writing, or, at the option of the investigator, in an informal conference. If an explanation is offered and accepted by the Center for Devices and Radiological Health, the disqualification process will be terminated. If an explanation is offered but not accepted by the Center for Devices and Radiological Health, the investigator will be given an opportunity for a regulatory hearing under part 16 of this chapter on the question of whether the investigator is entitled to receive investigational devices.

(b) After evaluating all available information, including any explanation presented by the investigator, if the Commissioner determines that the investigator has repeatedly or deliberately failed to comply with the requirements of this part, part 50, or part 56 of this chapter, or has deliberately or repeatedly submitted false information either to the sponsor of the investigation or in any required report, the Commissioner will notify the investigator, the sponsor of any investigation in which the investigator has been named as a participant, and the reviewing IRB that the investigator is not entitled to receive investigational devices. The notification will provide a statement of basis for such determination.

(c) Each investigational device exemption (IDE) and each cleared or approved application submitted under this part, subpart E of part 807 of this chapter, or part 814
of this chapter containing data reported by an investigator who has been determined to be ineligible to receive investigational devices will be examined to determine whether the investigator has submitted unreliable data that are essential to the continuation of the investigation or essential to the approval or clearance of any marketing application.

(d) If the Commissioner determines, after the unreliable data submitted by the investigator are eliminated from consideration, that the data remaining are inadequate to support a conclusion that it is reasonably safe to continue the investigation, the Commissioner will notify the sponsor who shall have an opportunity for a regulatory hearing under part 16 of this chapter. If a danger to the public health exists, however, the Commissioner shall terminate the IDE immediately and notify the sponsor and the reviewing IRB of the determination. In such case, the sponsor shall have an opportunity for a regulatory hearing before FDA under part 16 of this chapter on the question of whether the IDE should be reinstated.

(e) If the Commissioner determines, after the unreliable data submitted by the investigator are eliminated from consideration, that the continued clearance or approval of the marketing application for which the data were submitted cannot be justified, the Commissioner will proceed to withdraw approval or rescind clearance of the medical device in accordance with the applicable provisions of the act.

(f) An investigator who has been determined to be ineligible to receive investigational devices may be reinstated as eligible when the Commissioner determines that the investigator has presented adequate assurances that the investigator will employ investigational devices solely in compliance with the provisions of this part and of parts 50 and 56 of this chapter.


Subpart F [Reserved]

Subpart G--Records and Reports

§812.140 Records.

(a) Investigator records. A participating investigator shall maintain the following accurate, complete, and current records relating to the investigator's participation in an investigation:

(1) All correspondence with another investigator, an IRB, the sponsor, a monitor, or FDA, including required reports.

(2) Records of receipt, use or disposition of a device that relate to:
   (i) The type and quantity of the device, the dates of its receipt, and the batch number or code mark.
   (ii) The names of all persons who received, used, or disposed of each device.
   (iii) Why and how many units of the device have been returned to the sponsor, repaired, or otherwise disposed of.

(3) Records of each subject's case history and exposure to the device. Case histories include the case report forms and supporting data including, for example, signed and dated consent forms and medical records including, for example, progress
notes of the physician, the individual's hospital chart(s), and the nurses' notes. Such records shall include:

(i) Documents evidencing informed consent and, for any use of a device by the investigator without informed consent, any written concurrence of a licensed physician and a brief description of the circumstances justifying the failure to obtain informed consent. The case history for each individual shall document that informed consent was obtained prior to participation in the study.

(ii) All relevant observations, including records concerning adverse device effects (whether anticipated or unanticipated), information and data on the condition of each subject upon entering, and during the course of, the investigation, including information about relevant previous medical history and the results of all diagnostic tests.

(iii) A record of the exposure of each subject to the investigational device, including the date and time of each use, and any other therapy.

(4) The protocol, with documents showing the dates of and reasons for each deviation from the protocol.

(5) Any other records that FDA requires to be maintained by regulation or by specific requirement for a category of investigations or a particular investigation.

(b) Sponsor records. A sponsor shall maintain the following accurate, complete, and current records relating to an investigation:

(1) All correspondence with another sponsor, a monitor, an investigator, an IRB, or FDA, including required reports.

(2) Records of shipment and disposition. Records of shipment shall include the name and address of the consignee, type and quantity of device, date of shipment, and batch number or code mark. Records of disposition shall describe the batch number or code marks of any devices returned to the sponsor, repaired, or disposed of in other ways by the investigator or another person, and the reasons for and method of disposal.

(3) Signed investigator agreements including the financial disclosure information required to be collected under §812.43(c)(5) in accordance with part 54 of this chapter.

(4) For each investigation subject to §812.2(b)(1) of a device other than a significant risk device, the records described in paragraph (b)(5) of this section and the following records, consolidated in one location and available for FDA inspection and copying:

(i) The name and intended use of the device and the objectives of the investigation;

(ii) A brief explanation of why the device is not a significant risk device:

(iii) The name and address of each investigator:

(iv) The name and address of each IRB that has reviewed the investigation:

(v) A statement of the extent to which the good manufacturing practice regulation in part 820 will be followed in manufacturing the device; and

(vi) Any other information required by FDA.

(5) Records concerning adverse device effects (whether anticipated or unanticipated) and complaints and
(6) Any other records that FDA requires to be maintained by regulation or by specific requirement for a category of investigation or a particular investigation.

(c) IRB records. An IRB shall maintain records in accordance with part 56 of this chapter.

(d) Retention period. An investigator or sponsor shall maintain the records required by this subpart during the investigation and for a period of 2 years after the latter of the following two dates: The date on which the investigation is terminated or completed, or the date that the records are no longer required for purposes of supporting a premarket approval application or a notice of completion of a product development protocol.

(e) Records custody. An investigator or sponsor may withdraw from the responsibility to maintain records for the period required in paragraph (d) of this section and transfer custody of the records to any other person who will accept responsibility for them under this part, including the requirements of §812.145. Notice of a transfer shall be given to FDA not later than 10 working days after transfer occurs.


§812.145 Inspections.

(a) Entry and inspection. A sponsor or an investigator who has authority to grant access shall permit authorized FDA employees, at reasonable times and in a reasonable manner, to enter and inspect any establishment where devices are held (including any establishment where devices are manufactured, processed, packed, installed, used, or implanted or where records of results from use of devices are kept).

(b) Records inspection. A sponsor, IRB, or investigator, or any other person acting on behalf of such a person with respect to an investigation, shall permit authorized FDA employees, at reasonable times and in a reasonable manner, to inspect and copy all records relating to an investigation.

(c) Records identifying subjects. An investigator shall permit authorized FDA employees to inspect and copy records that identify subjects, upon notice that FDA has reason to suspect that adequate informed consent was not obtained, or that reports required to be submitted by the investigator to the sponsor or IRB have not been submitted or are incomplete, inaccurate, false, or misleading.

§812.150 Reports.

(a) Investigator reports. An investigator shall prepare and submit the following complete, accurate, and timely reports:

(1) Unanticipated adverse device effects. An investigator shall submit to the sponsor and to the reviewing IRB a report of any unanticipated adverse device effect occurring during an investigation as soon as possible, but in no event later than 10 working days after the investigator first learns of the effect.

(2) Withdrawal of IRB approval. An investigator shall report to the sponsor, within 5 working days, a withdrawal of approval by the reviewing IRB of the investigator’s part of an investigation.
(3) Progress. An investigator shall submit progress reports on the investigation to the sponsor, the monitor, and the reviewing IRB at regular intervals, but in no event less often than yearly.

(4) Deviations from the investigational plan. An investigator shall notify the sponsor and the reviewing IRB (see §56.108(a) (3) and (4)) of any deviation from the investigational plan to protect the life or physical well-being of a subject in an emergency. Such notice shall be given as soon as possible, but in no event later than 5 working days after the emergency occurred. Except in such an emergency, prior approval by the sponsor is required for changes in or deviations from a plan, and if these changes or deviations may affect the scientific soundness of the plan or the rights, safety, or welfare of human subjects, FDA and IRB in accordance with §812.35(a) also is required.

(5) Informed consent. If an investigator uses a device without obtaining informed consent, the investigator shall report such use to the sponsor and the reviewing IRB within 5 working days after the use occurs.

(6) Final report. An investigator shall, within 3 months after termination or completion of the investigation or the investigator's part of the investigation, submit a final report to the sponsor and the reviewing IRB.

(7) Other. An investigator shall, upon request by a reviewing IRB or FDA, provide accurate, complete, and current information about any aspect of the investigation.

(b) Sponsor reports. A sponsor shall prepare and submit the following complete, accurate, and timely reports:

(1) Unanticipated adverse device effects. A sponsor who conducts an evaluation of an unanticipated adverse device effect under §812.46(b) shall report the results of such evaluation to FDA and to all reviewing IRB's and participating investigators within 10 working days after the sponsor first receives notice of the effect. Thereafter the sponsor shall submit such additional reports concerning the effect as FDA requests.

(2) Withdrawal of IRB approval. A sponsor shall notify FDA and all reviewing IRB's and participating investigators of any withdrawal of approval of an investigation or a part of an investigation by a reviewing IRB within 5 working days after receipt of the withdrawal of approval.

(3) Withdrawal of FDA approval. A sponsor shall notify all reviewing IRB's and participating investigators of any withdrawal of FDA approval of the investigation, and shall do so within 5 working days after receipt of notice of the withdrawal of approval.

(4) Current investigator list. A sponsor shall submit to FDA, at 6- month intervals, a current list of the names and addresses of all investigators participating in the investigation. The sponsor shall submit the first such list 6 months after FDA approval.

(5) Progress reports. At regular intervals, and at least yearly, a sponsor shall submit progress reports to all reviewing IRB's. In the case of a significant risk device, a sponsor shall also submit progress reports to FDA. A sponsor of a treatment IDE shall submit semi-annual progress reports to all reviewing IRB's and FDA.
in accordance with §812.36(f) and annual reports in accordance with this section.

(6) Recall and device disposition. A sponsor shall notify FDA and all reviewing IRB's of any request that an investigator return, repair, or otherwise dispose of any units of a device. Such notice shall occur within 30 working days after the request is made and shall state why the request was made.

(7) Final report. In the case of a significant risk device, the sponsor shall notify FDA within 30 working days of the completion or termination of the investigation and shall submit a final report to FDA and all reviewing the IRB's and participating investigators within 6 months after completion or termination. In the case of a device that is not a significant risk device, the sponsor shall submit a final report to all reviewing IRB's within 6 months after termination or completion.

(8) Informed consent. A sponsor shall submit to FDA a copy of any report by an investigator under paragraph (a)(5) of this section of use of a device without obtaining informed consent, within 5 working days of receipt of notice of such use.

(9) Significant risk device determinations. If an IRB determines that a device is a significant risk device, and the sponsor had proposed that the IRB consider the device not to be a significant risk device, the sponsor shall submit to FDA a report of the IRB's determination within 5 working days after the sponsor first learns of the IRB's determination.

(10) Other. A sponsor shall, upon request by a reviewing IRB or FDA, provide accurate, complete, and current information about any aspect of the investigation.

21 CFR 814 PREMARKET APPROVAL OF MEDICAL DEVICES

[Revised as of April 1, 2002]

Subpart A--General

§814.1 Scope.
(a) This part implements section 515 of the act by providing procedures for the premarket approval of medical devices intended for human use.
(b) References in this part to regulatory sections of the Code of Federal Regulations are to chapter I of title 21, unless otherwise noted.
(c) This part applies to any class III medical device, unless exempt under section 520(g) of the act, that:
   (1) Was not on the market (introduced or delivered for introduction into commerce for commercial distribution) before May 28, 1976, and is not substantially equivalent to a device on the market before May 28, 1976, or to a device first marketed on, or after that date, which has been classified into class I or class II; or
   (2) Is required to have an approved premarket approval application (PMA) or a declared completed product development protocol under a regulation issued under section 515(b) of the act; or
   (3) Was regulated by FDA as a new drug or antibiotic drug before May 28, 1976, and therefore is governed by section 520(1) of the act.
(d) This part amends the conditions to approval for any PMA approved before the effective date of this part. Any condition to approval for an approved PMA that is inconsistent with this part is revoked. Any condition to approval for an approved PMA that is consistent with this part remains in effect.

§814.2 Purpose.
The purpose of this part is to establish an efficient and thorough device review process--
(a) To facilitate the approval of PMA's for devices that have been shown to be safe and effective and that otherwise meet the statutory criteria for approval; and
(b) To ensure the disapproval of PMA's for devices that have not been shown to be safe and effective or that do not otherwise meet the statutory criteria for approval. This part shall be construed in light of these objectives.

§814.3 Definitions. For the purposes of this part:
(b) FDA means the Food and Drug Administration.
(c) IDE means an approved or considered approved investigational device exemption under section 520(g) of the act and parts 812 and 813.
(d) **Master file** means a reference source that a person submits to FDA. A master file may contain detailed information on a specific manufacturing facility, process, methodology, or component used in the manufacture, processing, or packaging of a medical device.

(e) **PMA** means any premarket approval application for a class III medical device, including all information submitted with or incorporated by reference therein. “PMA” includes a new drug application for a device under section 520(1) of the act.

(f) **PMA amendment** means information an applicant submits to FDA to modify a pending PMA or a pending PMA supplement.

(g) **PMA supplement** means a supplemental application to an approved PMA for approval of a change or modification in a class III medical device, including all information submitted with or incorporated by reference therein.

(h) **Person** includes any individual, partnership, corporation, association, scientific or academic establishment, Government agency, or organizational unit thereof, or any other legal entity.

(i) **Statement of material fact** means a representation that tends to show that the safety or effectiveness of a device is more probable than it would be in the absence of such a representation. A false affirmation or silence or an omission that would lead a reasonable person to draw a particular conclusion as to the safety or effectiveness of a device also may be a false statement of material fact, even if the statement was not intended by the person making it to be misleading or to have any probative effect.

(j) **30-day PMA supplement** means a supplemental application to an approved PMA in accordance with §814.39(e).

(k) **Reasonable probability** means that it is more likely than not that an event will occur.

(l) **Serious, adverse health consequences** means any significant adverse experience, including those which may be either life-threatening or involve permanent or long-term injuries, but excluding injuries that are nonlife-threatening and that are temporary and reasonably reversible.

(m) **HDE** means a premarket approval application submitted pursuant to this subpart seeking a humanitarian device exemption from the effectiveness requirements of sections 514 and 515 of the act as authorized by section 520(m)(2) of the act.

(n) **HUD** (humanitarian use device) means a medical device intended to benefit patients in the treatment or diagnosis of a disease or condition that affects or is manifested in fewer than 4,000 individuals in the United States per year.


§814.9 Confidentiality of data and information in a premarket approval application (PMA) file.

(a) A “PMA file” includes all data and information submitted with or incorporated by reference in the PMA, any IDE incorporated into the PMA, any PMA supplement, any report under §814.82, any master file, or any other related submission. Any record in the PMA file will be available for public disclosure in accordance with the provisions of this section and part 20. The confidentiality of information in a color additive petition submitted as part of a PMA is governed by §71.15.
(b) The existence of a PMA file may not be disclosed by FDA before an approval order is issued to the applicant unless it previously has been publicly disclosed or acknowledged.

(c) If the existence of a PMA file has not been publicly disclosed or acknowledged, data or information in the PMA file are not available for public disclosure.

(d)

(1) If the existence of a PMA file has been publicly disclosed or acknowledged before an order approving, or an order denying approval of the PMA is issued, data or information contained in the file are not available for public disclosure before such order issues. FDA may, however, disclose a summary of portions of the safety and effectiveness data before an approval order or an order denying approval of the PMA issues if disclosure is relevant to public consideration of a specific pending issue.

(2) Notwithstanding paragraph (d)(1) of this section, FDA will make available to the public upon request the information in the IDE that was required to be filed in Docket Number 95S-0158 in the Dockets Management Branch (HFA-305), Food and Drug Administration, 12420 Parklawn Dr., rm. 1-23, Rockville, MD 20857, for investigations involving an exception from informed consent under §50.24 of this chapter. Persons wishing to request this information shall submit a request under the Freedom of Information Act.

(e) Upon issuance of an order approving, or an order denying approval of any PMA, FDA will make available to the public the fact of the existence of the PMA and a detailed summary of information submitted to FDA respecting the safety and effectiveness of the device that is the subject of the PMA and that is the basis for the order.

(f) After FDA issues an order approving, or an order denying approval of any PMA, the following data and information in the PMA file are immediately available for public disclosure:

(1) All safety and effectiveness data and information previously disclosed to the public, as such disclosure is defined in §20.81.

(2) Any protocol for a test or study unless the protocol is shown to constitute trade secret or confidential commercial or financial information under §20.61.

(3) Any adverse reaction report, product experience report, consumer complaint, and other similar data and information, after deletion of:

   (i) Any information that constitutes trade secret or confidential commercial or financial information under §20.61; and

   (ii) Any personnel, medical, and similar information disclosure of which would constitute a clearly unwarranted invasion of personal privacy under §20.63; provided, however, that except for the information that constitutes trade secret or confidential commercial or financial information under §20.61, FDA will disclose to a patient who requests a report all the information in the report concerning that patient.

(4) A list of components previously disclosed to the public, as such disclosure is defined in §20.81.

(5) An assay method or other analytical method, unless it does not serve any regulatory purpose and is shown to fall within the exemption in §20.61 for trade secret or confidential commercial or financial information.
(6) All correspondence and written summaries of oral discussions relating to the PMA file, in accordance with the provisions of §§20.103 and 20.104.

(g) All safety and effectiveness data and other information not previously disclosed to the public are available for public disclosure if any one of the following events occurs and the data and information do not constitute trade secret or confidential commercial or financial information under §20.61:

1. The PMA has been abandoned. FDA will consider a PMA abandoned if:
   (i)(A) The applicant fails to respond to a request for additional information within 180 days after the date FDA issues the request or
   (B) Other circumstances indicate that further work is not being undertaken with respect to it, and
   (ii) The applicant fails to communicate with FDA within 7 days after the date on which FDA notifies the applicant that the PMA appears to have been abandoned.
2. An order denying approval of the PMA has issued, and all legal appeals have been exhausted.
3. An order withdrawing approval of the PMA has issued, and all legal appeals have been exhausted.
4. The device has been reclassified.
5. The device has been found to be substantially equivalent to a class I or class II device.
6. The PMA is considered voluntarily withdrawn under §814.44(g).

(h) The following data and information in a PMA file are not available for public disclosure unless they have been previously disclosed to the public, as such disclosure is defined in §20.81, or they relate to a device for which a PMA has been abandoned and they no longer represent a trade secret or confidential commercial or financial information as defined in §20.61:

1. Manufacturing methods or processes, including quality control procedures.
2. Production, sales, distribution, and similar data and information, except that any compilation of such data and information aggregated and prepared in a way that does not reveal data or information which are not available for public disclosure under this provision is available for public disclosure.
3. Quantitative or semiquantitative formulas.


§814.15 Research conducted outside the United States.

(a) A study conducted outside the United States submitted in support of a PMA and conducted under an IDE shall comply with part 812. A study conducted outside the United States submitted in support of a PMA and not conducted under an IDE shall comply with the provisions in paragraph (b) or (c) of this section, as applicable.

(b) Research begun on or after effective date. FDA will accept studies submitted in support of a PMA which have been conducted outside the United States and begun on or after November 19, 1986, if the data are valid and the investigator has conducted the studies in conformance with the “Declaration of Helsinki” or the laws and regulations of the country in which the research is conducted, whichever accords greater protection to the human subjects. If the standards of the country are used, the
applicant shall state in detail any differences between those standards and the “Declaration of Helsinki” and explain why they offer greater protection to the human subjects.

(c) Research begun before effective date. FDA will accept studies submitted in support of a PMA which have been conducted outside the United States and begun before November 19, 1986, if FDA is satisfied that the data are scientifically valid and that the rights, safety, and welfare of human subjects have not been violated.

(d) As sole basis for marketing approval. A PMA based solely on foreign clinical data and otherwise meeting the criteria for approval under this part may be approved if:

(1) The foreign data are applicable to the U.S. population and U.S. medical practice;

(2) The studies have been performed by clinical investigators of recognized competence; and

(3) The data may be considered valid without the need for an on-site inspection by FDA or, if FDA considers such an inspection to be necessary, FDA can validate the data through an on-site inspection or other appropriate means.

(e) Consultation between FDA and applicants. Applicants are encouraged to meet with FDA officials in a “presubmission” meeting when approval based solely on foreign data will be sought.

(Approved by the Office of Management and Budget under control number 0910-0231)


§814.17 Service of orders.

Orders issued under this part will be served in person by a designated officer or employee of FDA on, or by registered mail to, the applicant or the designated agent at the applicant's or designated agent's last known address in FDA's records.

§814.19 Product development protocol (PDP).

A class III device for which a product development protocol has been declared completed by FDA under this chapter will be considered to have an approved PMA.

Subpart B--Premarket Approval Application (PMA)

§814.20 Application.

(a) The applicant or an authorized representative shall sign the PMA. If the applicant does not reside or have a place of business within the United States, the PMA shall be countersigned by an authorized representative residing or maintaining a place of business in the United States and shall identify the representative's name and address.

(b) Unless the applicant justifies an omission in accordance with paragraph (d) of this section, a PMA shall include:

(1) The name and address of the applicant.

(2) A that specifies the volume and page number for each item referred to in the table.

A PMA shall include separate sections on nonclinical laboratory studies and on clinical investigations involving human subjects. A PMA shall be submitted in six copies each bound in one or more numbered volumes of reasonable size. The applicant shall include information that it believes to be trade secret or
confidential commercial or financial information in all copies of the PMA and identify in at least one copy the information that it believes to be trade secret or confidential commercial or financial information.

(3) A summary in sufficient detail that the reader may gain a general understanding of the data and information in the application. The summary shall contain the following information:

(i) Indications for use. A general description of the disease or condition the device will diagnose, treat, prevent, cure, or mitigate, including a description of the patient population for which the device is intended.

(ii) Device description. An explanation of how the device functions, the basic scientific concepts that form the basis for the device, and the significant physical and performance characteristics of the device. A brief description of the manufacturing process should be included if it will significantly enhance the reader's understanding of the device. The generic name of the device as well as any proprietary name or trade name should be included.

(iii) Alternative practices and procedures. A description of existing alternative practices or procedures for diagnosing, treating, preventing, curing, or mitigating the disease or condition for which the device is intended.

(iv) Marketing history. A brief description of the foreign and U.S. marketing history, if any, of the device, including a list of all countries in which the device has been marketed and a list of all countries in which the device has been withdrawn from marketing for any reason related to the safety or effectiveness of the device. The description shall include the history of the marketing of the device by the applicant and, if known, the history of the marketing of the device by any other person.

(v) Summary of studies. An abstract of any information or report described in the PMA under paragraph (b)(8)(ii) of this section and a summary of the results of technical data submitted under paragraph (b)(6) of this section. Such summary shall include a description of the objective of the study, a description of the experimental design of the study, a brief description of how the data were collected and analyzed, and a brief description of the results, whether positive, negative, or inconclusive. This section shall include the following:

(A) A summary of the nonclinical laboratory studies submitted in the application;

(B) A summary of the clinical investigations involving human subjects submitted in the application including a discussion of subject selection and exclusion criteria, study population, study period, safety and effectiveness data, adverse reactions and complications, patient discontinuation, patient complaints, device failures and replacements, results of statistical analyses of the clinical investigations, contraindications and precautions for use of the device, and other information from the clinical investigations as appropriate (any investigation conducted under an IDE shall be identified as such).

(vi) Conclusions drawn from the studies. A discussion demonstrating that the data and information in the application constitute valid scientific evidence within the meaning of §860.7 and provide reasonable assurance that the
device is safe and effective for its intended use. A concluding discussion shall present benefit and risk considerations related to the device including a discussion of any adverse effects of the device on health and any proposed additional studies or surveillance the applicant intends to conduct following approval of the PMA.

(4) A complete description of:
   (i) The device, including pictorial representations;
   (ii) Each of the functional components or ingredients of the device if the device consists of more than one physical component or ingredient;
   (iii) The properties of the device relevant to the diagnosis, treatment, prevention, cure, or mitigation of a disease or condition;
   (iv) The principles of operation of the device; and
   (v) The methods used in, and the facilities and controls used for, the manufacture, processing, packing, storage, and, where appropriate, installation of the device, in sufficient detail so that a person generally familiar with current good manufacturing practice can make a knowledgeable judgment about the quality control used in the manufacture of the device.

(5) Reference to any performance standard under section 514 of the act or the Radiation Control for Health and Safety Act of 1968 (42 U.S.C. 263b et seq.) in effect or proposed at the time of the submission and to any voluntary standard that is relevant to any aspect of the safety or effectiveness of the device and that is known to or that should reasonably be known to the applicant. The applicant shall--
   (i) Provide adequate information to demonstrate how the device meets, or justify any deviation from, any performance standard established under section 514 of the act or under the Radiation Control for Health and Safety Act, and
   (ii) Explain any deviation from a voluntary standard.

(6) The following technical sections which shall contain data and information in sufficient detail to permit FDA to determine whether to approve or deny approval of the application:
   (i) A section containing results of the nonclinical laboratory studies with the device including microbiological, toxicological, immunological, biocompatibility, stress, wear, shelf life, and other laboratory or animal tests as appropriate. Information on nonclinical laboratory studies shall include a statement that each such study was conducted in compliance with part 58, or, if the study was not conducted in compliance with such regulations, a brief statement of the reason for the noncompliance.
   (ii) A section containing results of the clinical investigations involving human subjects with the device including clinical protocols, number of investigators and subjects per investigator, subject selection and exclusion criteria, study population, study period, safety and effectiveness data, adverse reactions and complications, patient discontinuation, patient complaints, device failures and replacements, tabulations of data from all individual subject report forms and copies of such forms for each subject.
who died during a clinical investigation or who did not complete the investigation, results of statistical analyses of the clinical investigations, device failures and replacements, contraindications and precautions for use of the device, and any other appropriate information from the clinical investigations. Any investigation conducted under an IDE shall be identified as such. Information on clinical investigations involving human subjects shall include the following:

(A) A statement with respect to each study that it either was conducted in compliance with the institutional review board regulations in part 56, or was not subject to the regulations under §56.104 or §56.105, and that it was conducted in compliance with the informed consent regulations in part 50; or if the study was not conducted in compliance with those regulations, a brief statement of the reason for the noncompliance.

(B) A statement that each study was conducted in compliance with part 812 or part 813 concerning sponsors of clinical investigations and clinical investigators, or if the study was not conducted in compliance with those regulations, a brief statement of the reason for the noncompliance.

(7) For a PMA supported solely by data from one investigation, a justification showing that data and other information from a single investigator are sufficient to demonstrate the safety and effectiveness of the device and to ensure reproducibility of test results.

(8)(i) A bibliography of all published reports not submitted under paragraph (b)(6) of this section, whether adverse or supportive, known to or that should reasonably be known to the applicant and that concern the safety or effectiveness of the device.

(ii) An identification, discussion, and analysis of any other data, information, or report relevant to an evaluation of the safety and effectiveness of the device known to or that should reasonably be known to the applicant from any source, foreign or domestic, including information derived from investigations other than those proposed in the application and from commercial marketing experience.

(iii) Copies of such published reports or unpublished information in the possession of or reasonably obtainable by the applicant if an FDA advisory committee or FDA requests.

(9) One or more samples of the device and its components, if requested by FDA. If it is impractical to submit a requested sample of the device, the applicant shall name the location at which FDA may examine and test one or more devices.

(10) Copies of all proposed labeling for the device. Such labeling may include, e.g., instructions for installation and any information, literature, or advertising that constitutes labeling under section 201(m) of the act.

(11) An environmental assessment under §25.20(n) prepared in the applicable format in §25.40, unless the action qualifies for exclusion under §25.30 or §25.34. If the applicant believes that the action qualifies for exclusion, the PMA shall under §25.15(a) and (d) provide information that establishes to FDA's
satisfaction that the action requested is included within the excluded category and meets the criteria for the applicable exclusion.

(12) A financial certification or disclosure statement or both as required by part 54 of this chapter.

(13) Such other information as FDA may request. If necessary, FDA will obtain the concurrence of the appropriate FDA advisory committee before requesting additional information.

(c) Pertinent information in FDA files specifically referred to by an applicant may be incorporated into a PMA by reference. Information in a master file or other information submitted to FDA by a person other than the applicant will not be considered part of a PMA unless such reference is authorized in writing by the person who submitted the information or the master file. If a master file is not referenced within 5 years after the date that it is submitted to FDA, FDA will return the master file to the person who submitted it.

(d) If the applicant believes that certain information required under paragraph (b) of this section to be in a PMA is not applicable to the device that is the subject of the PMA, and omits any such information from its PMA, the applicant shall submit a statement that identifies the omitted information and justifies the omission. The statement shall be submitted as a separate section in the PMA and identified in . If the justification for the omission is not accepted by the agency, FDA will so notify the applicant.

(e) The applicant shall periodically update its pending application with new safety and effectiveness information learned about the device from ongoing or completed studies that may reasonably affect an evaluation of the safety or effectiveness of the device or that may reasonably affect the statement of contraindications, warnings, precautions, and adverse reactions in the draft labeling. The update report shall be consistent with the data reporting provisions of the protocol. The applicant shall submit three copies of any update report and shall include in the report the number assigned by FDA to the PMA. These updates are considered to be amendments to the PMA. The time frame for review of a PMA will not be extended due to the submission of an update report unless the update is a major amendment under §814.37(c)(1). The applicant shall submit these reports--

(1) 3 months after the filing date,
(2) Following receipt of an approvable letter, and
(3) At any other time as requested by FDA.

(f) If a color additive subject to section 706 of the act is used in or on the device and has not previously been listed for such use, then, in lieu of submitting a color additive petition under part 71, at the option of the applicant, the information required to be submitted under part 71 may be submitted as part of the PMA. When submitted as part of the PMA, the information shall be submitted in three copies each bound in one or more numbered volumes of reasonable size. A PMA for a device that contains a color additive that is subject to section 706 of the act will not be approved until the color additive is listed for use in or on the device.

(g) FDA has issued a PMA guidance document to assist the applicant in the arrangement and content of a PMA. This guidance document is available on the Internet at http://www.fda.gov/cdrh/dsma/pmaman/front.html. This guidance document is also
available upon request from the Center for Devices and Radiological Health, Division of Small Manufacturers Assistance (HFZ-220), 1350 Piccard Dr., Rockville, MD 20850, FAX 301-443-8818.

(h) If you are sending a PMA, PMA amendment, PMA supplement, or correspondence with respect to a PMA, you must send it to the Document Mail Center (HFZ-401), Center for Devices and Radiological Health, Food and Drug Administration, 9200 Corporate Blvd., Rockville, MD 20850.


§814.37 PMA amendments and resubmitted PMA's.

(a) An applicant may amend a pending PMA or PMA supplement to revise existing information or provide additional information.

(b) FDA may request the applicant to amend a PMA or PMA supplement with any information regarding the device that is necessary for FDA or the appropriate advisory committee to complete the review of the PMA or PMA supplement.

(c) A PMA amendment submitted to FDA shall include the PMA or PMA supplement number assigned to the original submission and, if submitted on the applicant's own initiative, the reason for submitting the amendment. FDA may extend the time required for its review of the PMA, or PMA supplement, as follows:

(1) If the applicant on its own initiative or at FDA's request submits a major PMA amendment (e.g., an amendment that contains significant new data from a previously unreported study, significant updated data from a previously reported study, detailed new analyses of previously submitted data, or significant required information previously omitted), the review period may be extended up to 180 days.

(2) If an applicant declines to submit a major amendment requested by FDA, the review period may be extended for the number of days that elapse between the date of such request and the date that FDA receives the written response declining to submit the requested amendment.

(d) An applicant may on its own initiative withdraw a PMA or PMA supplement. If FDA requests an applicant to submit a PMA amendment and a written response to FDA's request is not received within 180 days of the date of the request, FDA will consider the pending PMA or PMA supplement to be withdrawn voluntarily by the applicant.

(e) An applicant may resubmit a PMA or PMA supplement after withdrawing it or after it is considered withdrawn under paragraph (d) of this section, or after FDA has refused to accept it for filing, or has denied approval of the PMA or PMA supplement. A resubmitted PMA or PMA supplement shall comply with the requirements of §814.20 or §814.39, respectively, and shall include the PMA number assigned to the original submission and the applicant's reasons for resubmission of the PMA or PMA supplement.

§814.39 PMA supplements.

(a) After FDA's approval of a PMA, an applicant shall submit a PMA supplement for review and approval by FDA before making a change affecting the safety or
effectiveness of the device for which the applicant has an approved PMA, unless the change is of a type for which FDA, under paragraph (e) of this section, has advised that an alternate submission is permitted or is of a type which, under section 515(d)(6)(A) of the act and paragraph (f) of this section, does not require a PMA supplement under this paragraph. While the burden for determining whether a supplement is required is primarily on the PMA holder, changes for which an applicant shall submit a PMA supplement include, but are not limited to, the following types of changes if they affect the safety or effectiveness of the device:

1. New indications for use of the device.
2. Labeling changes.
3. The use of a different facility or establishment to manufacture, process, or package the device.
5. Changes in packaging.
6. Changes in the performance or design specifications, circuits, components, ingredients, principle of operation, or physical layout of the device.
7. Extension of the expiration date of the device based on data obtained under a new or revised stability or sterility testing protocol that has not been approved by FDA. If the protocol has been approved, the change shall be reported to FDA under paragraph (b) of this section.

(b) An applicant may make a change in a device after FDA's approval of a PMA for the device without submitting a PMA supplement if the change does not affect the device's safety or effectiveness and the change is reported to FDA in postapproval periodic reports required as a condition to approval of the device, e.g., an editorial change in labeling which does not affect the safety or effectiveness of the device.

(c) All procedures and actions that apply to an application under §814.20 also apply to PMA supplements except that the information required in a supplement is limited to that needed to support the change. A summary under §814.20(b)(3) is required for only a supplement submitted for new indications for use of the device, significant changes in the performance or design specifications, circuits, components, ingredients, principles of operation, or physical layout of the device, or when otherwise required by FDA. The applicant shall submit three copies of a PMA supplement and shall include information relevant to the proposed changes in the device. A PMA supplement shall include a separate section that identifies each change for which approval is being requested and explains the reason for each such change. The applicant shall submit additional copies and additional information if requested by FDA. The time frames for review of, and FDA action on, a PMA supplement are the same as those provided in §814.40 for a PMA.

(d) (1) After FDA approves a PMA, any change described in paragraph (d)(2) of this section that enhances the safety of the device or the safety in the use of the device may be placed into effect by the applicant prior to the receipt under §814.17 of a written FDA order approving the PMA supplement provided that:
   (i) The PMA supplement and its mailing cover are plainly marked “Special PMA Supplement--Changes Being Effected”;}
(ii) The PMA supplement provides a full explanation of the basis for the changes;
(iii) The applicant has received acknowledgement from FDA of receipt of the supplement; and
(iv) The PMA supplement specifically identifies the date that such changes are being effected.

(2) The following changes are permitted by paragraph (d)(1) of this section:
(i) Labeling changes that add or strengthen a contraindication, warning, precaution, or information about an adverse reaction.
(ii) Labeling changes that add or strengthen an instruction that is intended to enhance the safe use of the device.
(iii) Labeling changes that delete misleading, false, or unsupported indications.
(iv) Changes in quality controls or manufacturing process that add a new specification or test method, or otherwise provide additional assurance of purity, identity, strength, or reliability of the device.

(e) FDA will identify a change to a device for which an applicant has an approved PMA and for which a PMA supplement under paragraph (a) is not required. FDA will identify such a change in an advisory opinion under §10.85, if the change applies to a generic type of device, or in correspondence to the applicant, if the change applies only to the applicant's device. FDA will require that a change for which a PMA supplement under paragraph (a) is not required be reported to FDA in--
(1) A periodic report under §814.84 or
(2) A 30-day PMA supplement under this paragraph.

(f) Under section 515(d) of the act, modifications to manufacturing procedures or methods of manufacture that affect the safety and effectiveness of a device subject to an approved PMA do not require submission of a PMA supplement under paragraph (a) of this section and are eligible to be the subject of a 30-day notice. A 30-day notice shall describe in detail the change, summarize the data or information supporting the change, and state that the change has been made in accordance with the requirements of part 820 of this chapter. The manufacturer may distribute the device 30 days after the date on which FDA receives the 30-day notice, unless FDA notifies the applicant within 30 days from receipt of the notice that the notice is not adequate. If the notice is not adequate, FDA shall inform the applicant in writing that a 135-day PMA supplement is needed and shall describe what further information or action is required for acceptance of such change. The number of days under review as a 30-day notice shall be deducted from the 135-day PMA supplement review period if the notice meets appropriate content requirements for a PMA supplement. FDA will identify, in the advisory opinion or correspondence, the type of information that is to be included in the report or 30-day PMA supplement. If the change is required to be reported to FDA in a periodic report, the change may be made before it is reported to FDA. If the change is required to be reported in a 30-day PMA supplement, the change may be made 30 days after FDA files the 30-day PMA supplement unless FDA requires the PMA holder to provide additional information, informs the PMA holder that the supplement is not approvable, or disapproves the supplement. The 30-day PMA supplement shall follow the instructions in the correspondence or advisory opinion. Any 30-day PMA supplement that does not meet the requirements of the
correspondence or advisory opinion will not be filed and, therefore, will not be deemed approved 30 days after receipt.


Subpart C--FDA Action on a PMA

§814.40 Time frames for reviewing a PMA.

Within 180 days after receipt of an application that is accepted for filing and to which the applicant does not submit a major amendment, FDA will review the PMA and, after receiving the report and recommendation of the appropriate FDA advisory committee, send the applicant an approval order under §814.44(d), an approvable letter under §814.44(e), a not approvable letter under §814.44(f), or an order denying approval under §814.45. The approvable letter and the not approvable letter will provide an opportunity for the applicant to amend or withdraw the application, or to consider the letter to be a denial of approval of the PMA under §814.45 and to request administrative review under section 515 (d)(3) and (g) of the act.

§814.42 Filing a PMA.

(a) The filing of an application means that FDA has made a threshold determination that the application is sufficiently complete to permit a substantive review. Within 45 days after a PMA is received by FDA, the agency will notify the applicant whether the application has been filed.

(b) If FDA does not find that any of the reasons in paragraph (e) of this section for refusing to file the PMA applies, the agency will file the PMA and will notify the applicant in writing of the filing. The notice will include the PMA reference number and the date FDA filed the PMA. The date of filing is the date that a PMA accepted for filing was received by the agency. The 180-day period for review of a PMA starts on the date of filing.

(c) If FDA refuses to file a PMA, the agency will notify the applicant of the reasons for the refusal. This notice will identify the deficiencies in the application that prevent filing and will include the PMA reference number.

(d) If FDA refuses to file the PMA, the applicant may:

(1) Resubmit the PMA with additional information necessary to comply with the requirements of section 515(c)(1) (A)-(G) of the act and §814.20. A resubmitted PMA shall include the PMA reference number of the original submission. If the resubmitted PMA is accepted for filing, the date of filing is the date FDA receives the resubmission;

(2) Request in writing within 10 working days of the date of receipt of the notice refusing to file the PMA, an informal conference with the Director of the Office of Device Evaluation to review FDA's decision not to file the PMA. FDA will hold the informal conference within 10 working days of its receipt of the request and will render its decision on filing within 5 working days after the informal conference. If, after the informal conference, FDA accepts the PMA for filing, the date of filing will be the date of the decision to accept the PMA for filing. If
FDA does not reverse its decision not to file the PMA, the applicant may request reconsideration of the decision from the Director of the Center for Devices and Radiological Health. The Director's decision will constitute final administrative action for the purpose of judicial review.

(e) FDA may refuse to file a PMA if any of the following applies:

1. The application is incomplete because it does not on its face contain all the information required under section 515(c)(1) (A)-(G) of the act;
2. The PMA does not contain each of the items required under §814.20 and justification for omission of any item is inadequate;
3. The applicant has a pending premarket notification under section 510(k) of the act with respect to the same device, and FDA has not determined whether the device falls within the scope of §814.1(c).
4. The PMA contains a false statement of material fact.
5. The PMA is not accompanied by a statement of either certification or disclosure as required by part 54 of this chapter.


§814.44 Procedures for review of a PMA.

(a) FDA will begin substantive review of a PMA after the PMA is accepted for filing under §814.42. FDA may refer the PMA to a panel on its own initiative, and will do so upon request of an applicant, unless FDA determines that the application substantially duplicates information previously reviewed by a panel. If FDA refers an application to a panel, FDA will forward the PMA, or relevant portions thereof, to each member of the appropriate FDA panel for review. During the review process, FDA may communicate with the applicant as set forth under §814.37(b), or with a panel to respond to questions that may be posed by panel members or to provide additional information to the panel. FDA will maintain a record of all communications with the applicant and with the panel.

(b) The advisory committee shall submit a report to FDA which includes the committee's recommendation and the basis for such recommendation on the PMA. Before submission of this report, the committee shall hold a public meeting to review the PMA in accordance with part 14. This meeting may be held by a telephone conference under §14.22(g). The advisory committee report and recommendation may be in the form of a meeting transcript signed by the chairperson of the committee.

(c) FDA will complete its review of the PMA and the advisory committee report and recommendation and, within the later of 180 days from the date of filing of the PMA under §814.42 or the number of days after the date of filing as determined under §814.37(c), issue an approval order under paragraph (d) of this section, an approvable letter under paragraph (e) of this section, a not approvable letter under paragraph (f) of this section, or an order denying approval of the application under §814.45(a).

(d) 1. FDA will issue to the applicant an order approving a PMA if none of the reasons in §814.45 for denying approval of the application applies. FDA will approve an application on the basis of draft final labeling if the only deficiencies in the application concern editorial or similar minor deficiencies in the draft final
labeling. Such approval will be conditioned upon the applicant incorporating the specified labeling changes exactly as directed and upon the applicant submitting to FDA a copy of the final printed labeling before marketing. FDA will also give the public notice of the order, including notice of and opportunity for any interested persons to request review under section 515(d)(3) of the act. The notice of approval will be placed on FDA's home page on the Internet (http://www.fda.gov), and it will state that a detailed summary of information respecting the safety and effectiveness of the device, which was the basis for the order approving the PMA, including information about any adverse effects of the device on health, is available on the Internet and has been placed on public display, and that copies are available upon request. FDA will publish in the Federal Register after each quarter a list of the approvals announced in that quarter. When a notice of approval is published, data and information in the PMA file will be available for public disclosure in accordance with §814.9.

(2) A request for copies of the current PMA approvals and denials document and for copies of summaries of safety and effectiveness shall be sent in writing to the Dockets Management Branch (HFA-305), Food and Drug Administration, 12420 Parklawn Dr., rm. 1-23, Rockville, MD 20857.

(e) FDA will send the applicant an approvable letter if the application substantially meets the requirements of this part and the agency believes it can approve the application if specific additional information is submitted or specific conditions are agreed to by the applicant.

(1) The approvable letter will describe the information FDA requires to be provided by the applicant or the conditions the applicant is required to meet to obtain approval. For example, FDA may require, as a condition to approval:

(i) The submission of certain information identified in the approvable letter, e.g., final labeling;

(ii) An FDA inspection that finds the manufacturing facilities, methods, and controls in compliance with part 820 and, if applicable, that verifies records pertinent to the PMA;

(iii) Restrictions imposed on the device under section 515(d)(1)(B)(ii) or 520(e) of the act;

(iv) Postapproval requirements as described in subpart E of this part.

(2) In response to an approvable letter the applicant may:

(i) Amend the PMA as requested in the approvable letter; or

(ii) Consider the approvable letter to be a denial of approval of the PMA under §814.45 and request administrative review under section 515(d)(3) of the act by filing a petition in the form of a petition for reconsideration under §10.33; or

(iii) Withdraw the PMA.

(f) FDA will send the applicant a not approvable letter if the agency believes that the application may not be approved for one or more of the reasons given in §814.45(a). The not approvable letter will describe the deficiencies in the application, including each applicable ground for denial under section 515(d)(2) (A)-(E) of the act, and, where practical, will identify measures required to place the PMA in approvable form. In response to a not approvable letter, the applicant may:
(1) Amend the PMA as requested in the not approvable letter (such an amendment will be considered a major amendment under §814.37(c)(1)); or
(2) Consider the not approvable letter to be a denial of approval of the PMA under §814.45 and request administrative review under section 515(d)(3) of the act by filing a petition in the form of a petition for reconsideration under §10.33; or
(3) Withdraw the PMA.

(g) FDA will consider a PMA to have been withdrawn voluntarily if:
(1) The applicant fails to respond in writing to a written request for an amendment within 180 days after the date FDA issues such request;
(2) The applicant fails to respond in writing to an approvable or not approvable letter within 180 days after the date FDA issues such letter; or
(3) The applicant submits a written notice to FDA that the PMA has been withdrawn.


§814.45 Denial of approval of a PMA.

(a) FDA may issue an order denying approval of a PMA if the applicant fails to follow the requirements of this part or if, upon the basis of the information submitted in the PMA or any other information before the agency, FDA determines that any of the grounds for denying approval of a PMA specified in section 515(d)(2) (A)-(E) of the act applies. In addition, FDA may deny approval of a PMA for any of the following reasons:
(1) The PMA contains a false statement of material fact;
(2) The device's proposed labeling does not comply with the requirements in part 801 or part 809;
(3) The applicant does not permit an authorized FDA employee an opportunity to inspect at a reasonable time and in a reasonable manner the facilities, controls, and to have access to and to copy and verify all records pertinent to the application;
(4) A nonclinical laboratory study that is described in the PMA and that is essential to show that the device is safe for use under the conditions prescribed, recommended, or suggested in its proposed labeling, was not conducted in compliance with the good laboratory practice regulations in part 58 and no reason for the noncompliance is provided or, if it is, the differences between the practices used in conducting the study and the good laboratory practice regulations do not support the validity of the study; or
(5) Any clinical investigation involving human subjects described in the PMA, subject to the institutional review board regulations in part 56 or informed consent regulations in part 50, was not conducted in compliance with those regulations such that the rights or safety of human subjects were not adequately protected.

(b) FDA will issue any order denying approval of the PMA in accordance with §814.17. The order will inform the applicant of the deficiencies in the PMA, including each applicable ground for denial under section 515(d)(2) of the act and the regulations under this part, and, where practical, will identify measures required to place the PMA in approvable form. The order will include a notice of an opportunity to request review under section 515(d)(3) of the act.
(c) FDA will use the criteria specified in §860.7 to determine the safety and effectiveness of a device in deciding whether to approve or deny approval of a PMA. FDA may use information other than that submitted by the applicant in making such determination.

(d)

(1) FDA will give the public notice of an order denying approval of the PMA. The notice will be placed on the FDA's home page on the Internet (http://www.fda.gov), and it will state that a detailed summary of information respecting the safety and effectiveness of the device, including information about any adverse effects of the device on health, is available on the Internet and has been placed on public display and that copies are available upon request. FDA will publish in the Federal Register after each quarter a list of the denials announced in that quarter. When a notice of denial of approval is made publicly available, data and information in the PMA file will be available for public disclosure in accordance with §814.9.

(2) A request for copies of the current PMA approvals and denials document and copies of summaries of safety and effectiveness shall be sent in writing to the Freedom of Information Staff (HFI-35), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857.

(e) FDA will issue an order denying approval of a PMA after an approvable or not approvable letter has been sent and the applicant:

(1) Submits a requested amendment but any ground for denying approval of the application under section 515(d)(2) of the act still applies; or

(2) Notifies FDA in writing that the requested amendment will not be submitted; or

(3) Petitions for review under section 515(d)(3) of the act by filing a petition in the form of a petition for reconsideration under §10.33.


§814.46 Withdrawal of approval of a PMA.

(a) FDA may issue an order withdrawing approval of a PMA if, from any information available to the agency, FDA determines that:

(1) Any of the grounds under section 515(e)(1) (A)-(G) of the act applies.

(2) Any postapproval requirement imposed by the PMA approval order or by regulation has not been met.

(3) A nonclinical laboratory study that is described in the PMA and that is essential to show that the device is safe for use under the conditions prescribed, recommended, or suggested in its proposed labeling, was not conducted in compliance with the good laboratory practice regulations in part 58 and no reason for the noncompliance is provided or, if it is, the differences between the practices used in conducting the study and the good laboratory practice regulations do not support the validity of the study.

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

(b)
(1) FDA may seek advice on scientific matters from any appropriate FDA advisory committee in deciding whether to withdraw approval of a PMA.
(2) FDA may use information other than that submitted by the applicant in deciding whether to withdraw approval of a PMA.
(c) Before issuing an order withdrawing approval of a PMA, FDA will issue the holder of the approved application a notice of opportunity for an informal hearing under part 16.
(d) If the applicant does not request a hearing or if after the part 16 hearing is held the agency decides to proceed with the withdrawal, FDA will issue to the holder of the approved application an order withdrawing approval of the application. The order will be issued under §814.17, will state each ground for withdrawing approval, and will include a notice of an opportunity for administrative review under section 515(e)(2) of the act.
(e) FDA will give the public notice of an order withdrawing approval of a PMA. The notice will be published in the Federal Register and will state that a detailed summary of information respecting the safety and effectiveness of the device, including information about any adverse effects of the device on health, has been placed on public display and that copies are available upon request. When a notice of withdrawal of approval is published, data and information in the PMA file will be available for public disclosure in accordance with §814.9.

§814.47 Temporary suspension of approval of a PMA.
(a) Scope.
(1) This section describes the procedures that FDA will follow in exercising its authority under section 515(e)(3) of the act (21 U.S.C. 360e(e)(3)). This authority applies to the original PMA, as well as any PMA supplement(s), for a medical device.
(2) FDA will issue an order temporarily suspending approval of a PMA if FDA determines that there is a reasonable probability that continued distribution of the device would cause serious, adverse health consequences or death.
(b) Regulatory hearing.
(1) If FDA believes that there is a reasonable probability that the continued distribution of a device subject to an approved PMA would cause serious, adverse health consequences or death, FDA may initiate and conduct a regulatory hearing to determine whether to issue an order temporarily suspending approval of the PMA.
(2) Any regulatory hearing to determine whether to issue an order temporarily suspending approval of a PMA shall be initiated and conducted by FDA pursuant to part 16 of this chapter. If FDA believes that immediate action to remove a dangerous device from the market is necessary to protect the public health, the agency may, in accordance with §16.60(h) of this chapter, waive, suspend, or modify any part 16 procedure pursuant to §10.19 of this chapter.
(3) FDA shall deem the PMA holder's failure to request a hearing within the timeframe specified by FDA in the notice of opportunity for hearing to be a waiver.
(c) Temporary suspension order. If the PMA holder does not request a regulatory hearing or if, after the hearing, and after consideration of the administrative record of the hearing, FDA determines that there is a reasonable probability that the continued distribution of a device under an approved PMA would cause serious, adverse health consequences or death, the agency shall, under the authority of section 515(e)(3) of the act, issue an order to the PMA holder temporarily suspending approval of the PMA.

(d) Permanent withdrawal of approval of the PMA. If FDA issues an order temporarily suspending approval of a PMA, the agency shall proceed expeditiously, but within 60 days, to hold a hearing on whether to permanently withdraw approval of the PMA in accordance with section 515(e)(1) of the act and the procedures set out in §814.46.

[61 FR 15190, Apr. 5, 1996]

Subpart D--Administrative Review [Reserved]

Subpart E--Postapproval Requirements

§814.80 General.

A device may not be manufactured, packaged, stored, labeled, distributed, or advertised in a manner that is inconsistent with any conditions to approval specified in the PMA approval order for the device.

§814.82 Postapproval requirements.

(a) FDA may impose postapproval requirements in a PMA approval order or by regulation at the time of approval of the PMA or by regulation subsequent to approval. Postapproval requirements may include as a condition to approval of the device:

(1) Restriction of the sale, distribution, or use of the device as provided by section 515(d)(1)(B)(ii) or 520(e) of the act.

(2) Continuing evaluation and periodic reporting on the safety, effectiveness, and reliability of the device for its intended use. FDA will state in the PMA approval order the reason or purpose for such requirement and the number of patients to be evaluated and the reports required to be submitted.

(3) Prominent display in the labeling of a device and in the advertising of any restricted device of warnings, hazards, or precautions important for the device's safe and effective use, including patient information, e.g., information provided to the patient on alternative modes of therapy and on risks and benefits associated with the use of the device.

(4) Inclusion of identification codes on the device or its labeling, or in the case of an implant, on cards given to patients if necessary to protect the public health.

(5) Maintenance of records that will enable the applicant to submit to FDA information needed to trace patients if such information is necessary to protect the public health. Under section 519(a)(4) of the act, FDA will require that the identity of any patient be disclosed in records maintained under this paragraph only to the extent required for the medical welfare of the individual, to
determine the safety or effectiveness of the device, or to verify a record, report, or information submitted to the agency.

(6) Maintenance of records for specified periods of time and organization and indexing of records into identifiable files to enable FDA to determine whether there is reasonable assurance of the continued safety and effectiveness of the device.

(7) Submission to FDA at intervals specified in the approval order of periodic reports containing the information required by §814.84(b).

(8) Batch testing of the device.

(9) Such other requirements as FDA determines are necessary to provide reasonable assurance, or continued reasonable assurance, of the safety and effectiveness of the device.

(b) An applicant shall grant to FDA access to any records and reports required under the provisions of this part, and shall permit authorized FDA employees to copy and verify such records and reports and to inspect at a reasonable time and in a reasonable manner all manufacturing facilities to verify that the device is being manufactured, stored, labeled, and shipped under approved conditions.

(c) Failure to comply with any postapproval requirement constitutes a ground for withdrawal of approval of a PMA.

(Approved by the Office of Management and Budget under control number 0910-0231)

§814.84 Reports.

(a) The holder of an approved PMA shall comply with the requirements of part 803 and with any other requirements applicable to the device by other regulations in this subchapter or by order approving the device.

(b) Unless FDA specifies otherwise, any periodic report shall:

(1) Identify changes described in §814.39(a) and changes required to be reported to FDA under §814.39(b).

(2) Contain a summary and bibliography of the following information not previously submitted as part of the PMA:

(i) Unpublished reports of data from any clinical investigations or nonclinical laboratory studies involving the device or related devices and known to or that reasonably should be known to the applicant.

(ii) Reports in the scientific literature concerning the device and known to or that reasonably should be known to the applicant. If, after reviewing the summary and bibliography, FDA concludes that the agency needs a copy of the unpublished or published reports, FDA will notify the applicant that copies of such reports shall be submitted.

(Approved by the Office of Management and Budget under control number 0910-0231)

Subparts F-G [Reserved]
Subpart H--Humanitarian Use Devices

§814.100 Purpose and scope.

Source: 61 FR 33244, June 26, 1996, unless otherwise noted.

(a) This subpart H implements section 520(m) of the act. The purpose of section 520(m) is, to the extent consistent with the protection of the public health and safety and with ethical standards, to encourage the discovery and use of devices intended to benefit patients in the treatment or diagnosis of diseases or conditions that affect or are manifested in fewer than 4,000 individuals in the United States per year. This subpart provides procedures for obtaining:

1. HUD designation of a medical device; and
2. Marketing approval for the HUD notwithstanding the absence of reasonable assurance of effectiveness that would otherwise be required under sections 514 and 515 of the act.

(b) Although a HUD may also have uses that differ from the humanitarian use, applicants seeking approval of any non-HUD use shall submit a PMA as required under §814.20, or a premarket notification as required under part 807 of this chapter.

(c) Obtaining marketing approval for a HUD involves two steps:

1. Obtaining designation of the device as a HUD from FDA's Office of Orphan Products Development, and
2. Submitting an HDE to the Office of Device Evaluation (ODE), Center for Devices and Radiological Health (CDRH).

(d) A person granted an exemption under section 520(m) of the act shall submit periodic reports as described in §814.126(b).

(e) FDA may suspend or withdraw approval of an HDE after providing notice and an opportunity for an informal hearing.

[61 FR 33244, June 26, 1996, as amended at 63 FR 59220, Nov. 3, 1998]

§814.102 Designation of HUD status.

(a) Request for designation. Prior to submitting an HDE application, the applicant shall submit a request for HUD designation to FDA's Office of Orphan Products Development. The request shall contain the following:

1. A statement that the applicant requests HUD designation for a rare disease or condition or a valid subset of a disease or condition which shall be identified with specificity;
2. The name and address of the applicant, the name of the applicant's primary contact person and/or resident agent, including title, address, and telephone number;
3. A description of the rare disease or condition for which the device is to be used, the proposed indication or indications for use of the device, and the reasons why such therapy is needed. If the device is proposed for an indication that represents a subset of a common disease or condition, a demonstration that the subset is medically plausible should be included;
(4) A description of the device and a discussion of the scientific rationale for the use of the device for the rare disease or condition; and

(5) Documentation, with appended authoritative references, to demonstrate that the device is designed to treat or diagnose a disease or condition that affects or is manifested in fewer than 4,000 people in the United States per year. If the device is for diagnostic purposes, the documentation must demonstrate that fewer than 4,000 patients per year would be subjected to diagnosis by the device in the United States. Authoritative references include literature citations in specialized medical journals, textbooks, specialized medical society proceedings, or governmental statistics publications. When no such studies or literature citations exist, the applicant may be able to demonstrate the prevalence of the disease or condition in the United States by providing credible conclusions from appropriate research or surveys.

(b) FDA action. Within 45 days of receipt of a request for HUD designation, FDA will take one of the following actions:

(1) Approve the request and notify the applicant that the device has been designated as a HUD based on the information submitted;

(2) Return the request to the applicant pending further review upon submission of additional information. This action will ensue if the request is incomplete because it does not on its face contain all of the information required under §814.102(a). Upon receipt of this additional information, the review period may be extended up to 45 days; or

(3) Disapprove the request for HUD designation based on a substantive review of the information submitted. FDA may disapprove a request for HUD designation if:
   (i) There is insufficient evidence to support the estimate that the disease or condition for which the device is designed to treat or diagnose affects or is manifested in fewer than 4,000 people in the United States per year;
   (ii) FDA determines that, for a diagnostic device, 4,000 or more patients in the United States would be subjected to diagnosis using the device per year; or
   (iii) FDA determines that the patient population defined in the request is not a medically plausible subset of a larger population.

(c) Revocation of designation. FDA may revoke a HUD designation if the agency finds that:

(1) The request for designation contained an untrue statement of material fact or omitted material information; or

(2) Based on the evidence available, the device is not eligible for HUD designation.

(d) Submission. The applicant shall submit two copies of a completed, dated, and signed request for HUD designation to: Office of Orphan Products Development (HF-35), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857.

§814.104 Original applications.

(a) United States applicant or representative. The applicant or an authorized representative shall sign the HDE. If the applicant does not reside or have a place of business within the United States, the HDE shall be countersigned by an authorized representative residing or maintaining a place of business in the United States and shall identify the representative's name and address.
(b) Contents. Unless the applicant justifies an omission in accordance with paragraph (d) of this section, an HDE shall include:

(1) A copy of or reference to the determination made by FDA's Office of Orphan Products Development (in accordance with §814.102) that the device qualifies as a HUD;

(2) An explanation of why the device would not be available unless an HDE were granted and a statement that no comparable device (other than another HUD approved under this subpart or a device under an approved IDE) is available to treat or diagnose the disease or condition. The application also shall contain a discussion of the risks and benefits of currently available devices or alternative forms of treatment in the United States;

(3) An explanation of why the probable benefit to health from the use of the device outweighs the risk of injury or illness from its use, taking into account the probable risks and benefits of currently available devices or alternative forms of treatment. Such explanation shall include a description, explanation, or theory of the underlying disease process or condition, and known or postulated mechanism(s) of action of the device in relation to the disease process or condition;

(4) All of the information required to be submitted under §814.20(b), except that:

   (i) In lieu of the summaries, conclusions, and results from clinical investigations required under §§814.20(b)(3)(v)(B), (b)(3)(vi), and (b)(6)(ii), the applicant shall include the summaries, conclusions, and results of all clinical experience or investigations (whether adverse or supportive) reasonably obtainable by the applicant that are relevant to an assessment of the risks and probable benefits of the device; and

   (ii) In addition to the proposed labeling requirement set forth in §814.20(b)(10), the labeling shall bear the following statement: Humanitarian Device. Authorized by Federal law for use in the [treatment or diagnosis] of [specify disease or condition]. The effectiveness of this device for this use has not been demonstrated; and

(5) The amount to be charged for the device and, if the amount is more than $250, a report by an independent certified public accountant, made in accordance with the Statement on Standards for Attestation established by the American Institute of Certified Public Accountants, or in lieu of such a report, an attestation by a responsible individual of the organization, verifying that the amount charged does not exceed the costs of the device's research, development, fabrication, and distribution. If the amount charged is $250 or less, the requirement for a report by an independent certified public accountant or an attestation by a responsible individual of the organization is waived.

(c) Omission of information. If the applicant believes that certain information required under paragraph (b) of this section is not applicable to the device that is the subject of the HDE, and omits any such information from its HDE, the applicant shall submit a statement that identifies and justifies the omission. The statement shall be submitted as a separate section in the HDE and identified in the table of contents. If the justification for the omission is not accepted by the agency, FDA will so notify the applicant.
(d) Address for submissions and correspondence. Copies of all original HDE's, amendments and supplements, as well as any correspondence relating to an HDE, shall be sent or delivered to the Document Mail Center (HFZ-401), Office of Device Evaluation, Center for Devices and Radiological Health, Food and Drug Administration, 9200 Corporate Blvd., Rockville, MD 20850.

[61 FR 33244, June 26, 1996, as amended at 63 FR 59220, Nov. 3, 1998]

§814.106 HDE amendments and resubmitted HDE's.
An HDE or HDE supplement may be amended or resubmitted upon an applicant's own initiative, or at the request of FDA, for the same reasons and in the same manner as prescribed for PMA's in §814.37, except that the timeframes set forth in §814.37(c)(1) and (d) do not apply. If FDA requests an HDE applicant to submit an HDE amendment, and a written response to FDA's request is not received within 75 days of the date of the request, FDA will consider the pending HDE or HDE supplement to be withdrawn voluntarily by the applicant. Furthermore, if the HDE applicant, on its own initiative or at FDA's request, submits a major amendment as described in §814.37(c)(1), the review period may be extended up to 75 days.

[63 FR 59220, Nov. 3, 1998]

§814.108 Supplemental applications.
After FDA approval of an original HDE, an applicant shall submit supplements in accordance with the requirements for PMA's under §814.39, except that a request for a new indication for use of a HUD shall comply with requirements set forth in §814.110. The timeframes for review of, and FDA action on, an HDE supplement are the same as those provided in §814.114 for an HDE.

[63 FR 59220, Nov. 3, 1998]

§814.110 New indications for use.
(a) An applicant seeking a new indication for use of a HUD approved under this subpart H shall obtain a new designation of HUD status in accordance with §814.102 and shall submit an original HDE in accordance with §814.104.

(b) An application for a new indication for use made under §814.104 may incorporate by reference any information or data previously submitted to the agency under an HDE.

§814.112 Filing an HDE.
(a) The filing of an HDE means that FDA has made a threshold determination that the application is sufficiently complete to permit substantive review. Within 30 days from the date an HDE is received by FDA, the agency will notify the applicant whether the application has been filed. FDA may refuse to file an HDE if any of the following applies:

   (1) The application is incomplete because it does not on its face contain all the information required under §814.104(b);

   (2) FDA determines that there is a comparable device available (other than another HUD approved under this subpart or a device under an approved IDE) to treat
or diagnose the disease or condition for which approval of the HUD is being sought; or

(3) The application contains an untrue statement of material fact or omits material information.

(4) The HDE is not accompanied by a statement of either certification or disclosure, or both, as required by part 54 of this chapter.

(b) The provisions contained in §814.42(b), (c), and (d) regarding notification of filing decisions, filing dates, the start of the 75-day review period, and applicant's options in response to FDA refuse to file decisions shall apply to HDE's.


§814.114 Timeframes for reviewing an HDE.

Within 75 days after receipt of an HDE that is accepted for filing and to which the applicant does not submit a major amendment, FDA shall send the applicant an approval order, an approvable letter, a not approvable letter (under §814.116), or an order denying approval (under §814.118).

[63 FR 59221, Nov. 3, 1998]

§814.116 Procedures for review of an HDE.

(a) Substantive review. FDA will begin substantive review of an HDE after the HDE is accepted for filing under §814.112. FDA may refer an original HDE application to a panel on its own initiative, and shall do so upon the request of an applicant, unless FDA determines that the application substantially duplicates information previously reviewed by a panel. If the HDE is referred to a panel, the agency shall follow the procedures set forth under §814.44, with the exception that FDA will complete its review of the HDE and the advisory committee report and recommendations within 75 days from receipt of an HDE that is accepted for filing under §814.112 or the date of filing as determined under §814.106, whichever is later. Within the later of these two timeframes, FDA will issue an approval order under paragraph (b) of this section, an approvable letter under paragraph (c) of this section, a not approvable letter under paragraph (d) of this section, or an order denying approval of the application under §814.118(a).

(b) Approval order. FDA will issue to the applicant an order approving an HDE if none of the reasons in §814.118 for denying approval of the application applies. FDA will approve an application on the basis of draft final labeling if the only deficiencies in the application concern editorial or similar minor deficiencies in the draft final labeling. Such approval will be conditioned upon the applicant incorporating the specified labeling changes exactly as directed and upon the applicant submitting to FDA a copy of the final printed labeling before marketing. The notice of approval of an HDE will be published in the Federal Register in accordance with the rules and policies applicable to PMA's submitted under §814.20. Following the issuance of an approval order, data and information in the HDE file will be available for public disclosure in accordance with §814.9(b) through (h), as applicable.

(c) Approvable letter. FDA will send the applicant an approvable letter if the application substantially meets the requirements of this subpart and the agency believes it can
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approve the application if specific additional information is submitted or specific
conditions are agreed to by the applicant. The approvable letter will describe the
information FDA requires to be provided by the applicant or the conditions the
applicant is required to meet to obtain approval. For example, FDA may require as a
condition to approval:
(1) The submission of certain information identified in the approvable letter, e.g.,
final labeling;
(2) Restrictions imposed on the device under section 520(e) of the act;
(3) Postapproval requirements as described in subpart E of this part; and
(4) An FDA inspection that finds the manufacturing facilities, methods, and controls
in compliance with part 820 of this chapter and, if applicable, that verifies
records pertinent to the HDE.
(d) Not approvable letter. FDA will send the applicant a not approvable letter if the
agency believes that the application may not be approved for one or more of the
reasons given in §814.118. The not approvable letter will describe the deficiencies in
the application and, where practical, will identify measures required to place the HDE
in approvable form. The applicant may respond to the not approvable letter in the
same manner as permitted for not approvable letters for PMA's under §814.44(f),
with the exception that if a major HDE amendment is submitted, the review period
may be extended up to 75 days.
(e) FDA will consider an HDE to have been withdrawn voluntarily if:
(1) The applicant fails to respond in writing to a written request for an amendment
within 75 days after the date FDA issues such request;
(2) The applicant fails to respond in writing to an approvable or not approvable letter
within 75 days after the date FDA issues such letter; or
(3) The applicant submits a written notice to FDA that the HDE has been withdrawn.


§814.118 Denial of approval or withdrawal of approval of an HDE.

(a) FDA may deny approval or withdraw approval of an application if the applicant fails
to meet the requirements of section 520(m) of the act or of this part, or of any
condition of approval imposed by an IRB or by FDA, or any postapproval
requirements imposed under §814.126. In addition, FDA may deny approval or
withdraw approval of an application if, upon the basis of the information submitted in
the HDE or any other information before the agency, FDA determines that:
(1) There is a lack of a showing of reasonable assurance that the device is safe under
the conditions of use prescribed, recommended, or suggested in the labeling
thereof;
(2) The device is ineffective under the conditions of use prescribed, recommended, or
suggested in the labeling thereof;
(3) The applicant has not demonstrated that there is a reasonable basis from which to
conclude that the probable benefit to health from the use of the device
outweighs the risk of injury or illness, taking into account the probable risks and
benefits of currently available devices or alternative forms of treatment;
(4) The application or a report submitted by or on behalf of the applicant contains an
untrue statement of material fact, or omits material information;

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(5) The device's labeling does not comply with the requirements in part 801 or part 809 of this chapter;
(6) A nonclinical laboratory study that is described in the HDE and that is essential to show that the device is safe for use under the conditions prescribed, recommended, or suggested in its proposed labeling, was not conducted in compliance with the good laboratory practice regulations in part 58 of this chapter and no reason for the noncompliance is provided or, if it is, the differences between the practices used in conducting the study and the good laboratory practice regulations do not support the validity of the study;
(7) Any clinical investigation involving human subjects described in the HDE, subject to the institutional review board regulations in part 56 of this chapter or the informed consent regulations in part 50 of this chapter, was not conducted in compliance with those regulations such that the rights or safety of human subjects were not adequately protected;
(8) The applicant does not permit an authorized FDA employee an opportunity to inspect at a reasonable time and in a reasonable manner the facilities and controls, and to have access to and to copy and verify all records pertinent to the application; or
(9) The device's HUD designation should be revoked in accordance with §814.102(c).

(b) If FDA issues an order denying approval of an application, the agency will comply with the same notice and disclosure provisions required for PMA's under §814.45(b) and (d), as applicable.

(c) FDA will issue an order denying approval of an HDE after an approvable or not approvable letter has been sent and the applicant:
   (1) Submits a requested amendment but any ground for denying approval of the application under §814.118(a) still applies;
   (2) Notifies FDA in writing that the requested amendment will not be submitted; or
   (3) Petitions for review under section 515(d)(3) of the act by filing a petition in the form of a petition for reconsideration under §10.33 of this chapter.

(d) Before issuing an order withdrawing approval of an HDE, FDA will provide the applicant with notice and an opportunity for a hearing as required for PMA's under §814.46(c) and (d), and will provide the public with notice in accordance with §814.46(e), as applicable.


§814.120 Temporary suspension of approval of an HDE.
An HDE or HDE supplement may be temporarily suspended for the same reasons and in the same manner as prescribed for PMA's in §814.47.

[63 FR 59221, Nov. 3, 1998]

§814.122 Confidentiality of data and information.
(a) Requirement for disclosure. The “HDE file” includes all data and information submitted with or referenced in the HDE, any IDE incorporated into the HDE, any HDE amendment or supplement, any report submitted under §814.126, any master file, or any other related submission. Any record in the HDE file will be available for
public disclosure in accordance with the provisions of this section and part 20 of this chapter.

(b) Extent of disclosure. Disclosure by FDA of the existence and contents of an HDE file shall be subject to the same rules that pertain to PMA's under §814.9(b) through (h), as applicable.

§814.124 Institutional Review Board requirements.

(a) IRB approval. The HDE holder is responsible for ensuring that a HUD approved under this subpart is administered only in facilities having an Institutional Review Board (IRB) constituted and acting pursuant to part 56 of this chapter, including continuing review of use of the device. In addition, a HUD may be administered only if such use has been approved by the IRB located at the facility or by a similarly constituted IRB that has agreed to oversee such use and to which the local IRB has deferred in a letter to the HDE holder, signed by the IRB chair or an authorized designee. If, however, a physician in an emergency situation determines that approval from an IRB cannot be obtained in time to prevent serious harm or death to a patient, a HUD may be administered without prior approval by the IRB located at the facility or by a similarly constituted IRB that has agreed to oversee such use. In such an emergency situation, the physician shall, within 5 days after the use of the device, provide written notification to the chairman of the IRB of such use. Such written notification shall include the identification of the patient involved, the date on which the device was used, and the reason for the use.

(b) Withdrawal of IRB approval. A holder of an approved HDE shall notify FDA of any withdrawal of approval for the use of a HUD by a reviewing IRB within 5 working days after being notified of the withdrawal of approval.


§814.126 Postapproval requirements and reports.

(a) An HDE approved under this subpart H shall be subject to the postapproval requirements and reports set forth under subpart E of this part, as applicable, with the exception of §814.82(a)(7). In addition, medical device reports submitted to FDA in compliance with the requirements of part 803 of this chapter shall also be submitted to the IRB of record.

(b) In addition to the reports identified in paragraph (a) of this section, the holder of an approved HDE shall prepare and submit the following complete, accurate, and timely reports:

(1) Periodic reports. An HDE applicant is required to submit reports in accordance with the approval order. Unless FDA specifies otherwise, any periodic report shall include:

(i) An update of the information required under §814.102(a) in a separately bound volume;

(ii) An update of the information required under §814.104(b)(2), (b)(3), and (b)(5);

(iii) The number of devices that have been shipped or sold since initial marketing approval under this subpart H and, if the number shipped or
sold exceeds 4,000, an explanation and estimate of the number of devices used per patient. If a single device is used on multiple patients, the applicant shall submit an estimate of the number of patients treated or diagnosed using the device together with an explanation of the basis for the estimate;

(iv) Information describing the applicant's clinical experience with the device since the HDE was initially approved. This information shall include safety information that is known or reasonably should be known to the applicant, medical device reports made under part 8dd of this chapter, any data generated from the postmarketing studies, and information (whether published or unpublished) that is known or reasonably expected to be known by the applicant that may affect an evaluation of the safety of the device or that may affect the statement of contraindications, warnings, precautions, and adverse reactions in the device's labeling; and

(v) A summary of any changes made to the device in accordance with supplements submitted under §814.108. If information provided in the periodic reports, or any other information in the possession of FDA, gives the agency reason to believe that a device raises public health concerns or that the criteria for exemption are no longer met, the agency may require the HDE holder to submit additional information to demonstrate continued compliance with the HDE requirements.

(2) Other. An HDE holder shall maintain records of the names and addresses of the facilities to which the HUD has been shipped, correspondence with reviewing IRB's, as well as any other information requested by a reviewing IRB or FDA. Such records shall be maintained in accordance with the HDE approval order.

FEDERAL FOOD, DRUG, AND COSMETIC ACT
Excerpted

CHAPTER I - SHORT TITLE

SEC. 1. Short title.
This chapter may be cited as the Federal Food, Drug, and Cosmetic Act.

CHAPTER II - DEFINITIONS¹

SEC. 201. [321] For the purposes of this chapter -

(a) (1) The term "State", except as used in the last sentence of section 372(a) of this title, means any State or Territory of the United States, the District of Columbia, and the Commonwealth of Puerto Rico.
(2) The term "Territory" means any Territory or possession of the United States, including the District of Columbia, and excluding the Commonwealth of Puerto Rico and the Canal Zone.
(b) The term "interstate commerce" means
(1) commerce between any State or Territory and any place outside thereof, and
(2) commerce within the District of Columbia or within any other Territory not organized with a legislative body.
(c) The term "Department" means Department of Health and Human Services.
(d) The term "Secretary" means the Secretary of Health and Human Services.
(e) The term "person" includes individual, partnership, corporation, and association.
(f) The term "food" means
(1) articles used for food or drink for man or other animals,
(2) chewing gum, and
(3) articles used for components of any such article.
(g) The term "drug" means
(1) articles recognized in the official United States Pharmacopoeia, official Homoeopathic Pharmacopoeia of the United States, or official National Formulary, or any supplement to any of them; and
(B) articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals; and
(C) articles (other than food) intended to affect the structure or any function of the body of man or other animals; and
(D) articles intended for use as a component of any article specified in clause (A), (B), or (C). A food or dietary supplement for which a claim, subject to sections 403(r)(1)(B) and 403(r)(3) of this title or sections 403(r)(1)(B) and 403(r)(5)(D) of this title, is made in accordance with the requirements of section 403(r) of this title is not a drug solely because the label or the
labeling contains such a claim. A food, dietary ingredient, or dietary supplement for which a truthful and not misleading statement is made in accordance with section 403(r)(6) of this title is not a drug under clause (C) solely because the label or the labeling contains such a statement.

(2) The term "counterfeit drugs" means a drug which, or the container or labeling of which, without authorization, bears the trademark, trade name, or other identifying mark, imprint, or device, or any likeness thereof, of a drug manufacturer, processor, packer, or distributor other than the person or persons who in fact manufactured, processed, packed, or distributed such drug and which thereby falsely purports or is represented to be the product of, or to have been packed or distributed by, such other drug manufacturer, processor, packer, or distributor.

(h) The term "device" (except when used in paragraph (n) of this section and in sections 301(i), 403(f), 502(c), and 602(c)) means an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including any component, part, or accessory, which is -

(1) recognized in the official National Formulary, or the United States Pharmacopeia, or any supplement to them,
(2) intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, or
(3) intended to affect the structure or any function of the body of man or other animals, and which does not achieve its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of its primary intended purposes.

(i) The term "cosmetic" means

(1) articles intended to be rubbed, poured, sprinkled, or sprayed on, introduced into, or otherwise applied to the human body or any part thereof for cleansing, beautifying, promoting attractiveness, or altering the appearance, and
(2) articles intended for use as a component of any such articles; except that such term shall not include soap.

(j) The term "official compendium" means the official United States Pharmacopoeia, official Homeopathic Pharmacopoeia of the United States, official National Formulary, or any supplement to any of them.

(k) The term "label" means a display of written, printed, or graphic matter upon the immediate container of any article; and a requirement made by or under authority of this Act that any word, statement, or other information appear on the label shall not be considered to be complied with unless such word, statement, or other information also appears on the outside container or wrapper, if any there be, of the retail package of such article, or is easily legible through the outside container or wrapper.

(l) The term "immediate container" does not include package liners.

(m) The term "labeling" means all labels and other written, printed, or graphic matter upon any article or any of its containers or wrappers, or accompanying such article.

(n) If an article is alleged to be misbranded because the labeling or advertising is misleading, then in determining whether the labeling or advertising is misleading...
there shall be taken into account (among other things) not only representations made or suggested by statement, word, design, device, or any combination thereof, but also the extent to which the labeling or advertising fails to reveal facts material in the light of such representations or material with respect to consequences which may result from the use of the article to which the labeling or advertising relates under the conditions of use prescribed in the labeling or advertising thereof or under such conditions of use as are customary or usual.

(o) The representation of a drug, in its labeling, as an antiseptic shall be considered to be a representation that it is a germicide, except in the case of a drug purporting to be, or represented as, an antiseptic for inhibitory use as a wet dressing, ointment, dusting powder, or such other use as involves prolonged contact with the body.

(p) The term "new drug" means -

(1) Any drug (except a new animal drug or an animal feed bearing or containing a new animal drug) the composition of which is such that such drug is not generally recognized, among experts qualified by scientific training and experience to evaluate the safety and effectiveness of drugs, as safe and effective for use under the conditions prescribed, recommended, or suggested in the labeling thereof, except that such a drug not so recognized shall not be deemed to be a "new drug" if at any time prior to the enactment of this Act it was subject to the Food and Drugs Act of June 30, 1906, as amended, and if at such time its labeling contained the same representations concerning the conditions of its use; or

(2) Any drug (except a new animal drug or an animal feed bearing or containing a new animal drug) the composition of which is such that such drug, as a result of investigations to determine its safety and effectiveness for use under such conditions, has become so recognized, but which has not, otherwise than in such investigations, been used to a material extent or for a material time under such conditions.

(q)

(1) The term "pesticide chemical" means any substance that is a pesticide within the meaning of the Federal Insecticide, Fungicide, and Rodenticide Act, including all active and inert ingredients of such pesticide.

(2) The term "pesticide chemical residue" means a residue in or on raw agricultural commodity or processed food of -

(A) a pesticide chemical; or

(B) any other added substance that is present on or in the commodity or food primarily as a result of the metabolism or other degradation of a pesticide chemical.

(3) Notwithstanding paragraphs (1) and (2), the Administrator may by regulation except a substance from the definition of "pesticide chemical" or "pesticide chemical residue" if-

(A) its occurrence as a residue on or in a raw agricultural commodity or processed food is attributable primarily to natural causes or to human activities not involving the use of any substances for a pesticidal purpose in the production, storage, processing, or transportation of any raw agricultural commodity or processed food; and
(B) the Administrator, after consultation with the Secretary, determines that the substance more appropriately should be regulated under one or more provisions of this Act other than sections 402(a)(2)(B) and 408.

(r) The term "raw agricultural commodity" means any food in its raw or natural state, including all fruits that are washed, colored, or otherwise treated in their unpeeled natural form prior to marketing.

(s) The term "food additive" means any substance the intended use of which results or may reasonably be expected to result, directly or indirectly, in its becoming a component or otherwise affecting the characteristics of any food (including any substance intended for use in producing, manufacturing, packing, processing, preparing, treating, packaging, transporting, or holding food; and including any source of radiation intended for any such use), if such substance is not generally recognized, among experts qualified by scientific training and experience to evaluate its safety, as having been adequately shown through scientific procedures (or, in the case as a substance used in food prior to January 1, 1958, through either scientific procedures or experience based on common use in food) to be safe under the conditions of its intended use; except that such term does not include -

(1) a pesticide chemical in or on a raw agricultural commodity; or processed food; or
(2) a pesticide chemical; or
(3) a color additive; or
(4) any substance used in accordance with a sanction or approval granted prior to the enactment of this paragraph¹ (footnote 2) pursuant to this Act, the Poultry Products Inspection Act (21 U.S.C. 451 and the following) or the Meat Inspection Act of March 4, 1907, (34 Stat 1260) as amended and extended (21 U.S.C. 71 and the following);
(5) a new animal drug; or
(6) an ingredient described in paragraph (ff) in, or intended for use in, a dietary supplement.

(t)

(1) The term "color additive" means a material which -

(A) is a dye, pigment, or other substance made by a process of synthesis or similar artifice, or extracted, isolated, or otherwise derived, with or without intermediate or final change of identity, from a vegetable, animal, mineral, or other source, and

(B) when added or applied to a food, drug, or cosmetic, or to the human body or any part thereof, is capable (alone or through reaction with other substance) of imparting color thereto; except that such term does not include any material which the Secretary, by regulation, determines is used (or intended to be used) solely for a purpose or purposes other than coloring.

(2) The term "color" includes black, white, and intermediate grays.

(3) Nothing in subparagraph (1) of this paragraph shall be construed to apply to any pesticide chemical, soil or plant nutrient, or other agricultural chemical solely because of its effect in aiding, retarding, or otherwise affecting, directly or indirectly, the growth or other natural physiological processes of produce of the soil and thereby affecting its color, whether before or after harvest.
(u) The term "safe" as used in paragraph (s) of this section and in sections 409, 512, and 721 of this title, has reference to the health of man or animal.

(v) The term "new animal drug" means any drug intended for use for animals other than man, including any drug intended for use in animal feed but not including such animal feed -

(1) the composition of which is such that such drug is not generally recognized, among experts qualified by scientific training and experience to evaluate the safety and effectiveness of animal drugs, as safe and effective for use under the conditions prescribed, recommended, or suggested in the labeling thereof; except that such a drug not so recognized shall not be deemed to be a "new animal drug" if at any time prior to June 25, 1938, it was subject to the Food and Drug Act of June 30, 1906, as amended, and if at such time its labeling contained the same representations concerning the conditions of its use; or

(2) the composition of which is such that such drug, as a result of investigations to determine its safety and effectiveness for use under such conditions, has become so recognized but which has not, otherwise than in such investigations, been used to a material extent or for a material time under such conditions.

(w) The term "animal feed", as used in paragraph (w)' (Footnote 3) of this section, in section 512 of this title, and in provisions of this Act referring to such paragraph or section, means an article which is intended for use for food for animals other than man and which is intended for use as a substantial source of nutrients in the diet of the animal, and is not limited to a mixture intended to be the sole ration of the animal.

(x) The term "informal hearing" means a hearing which is not subject to section 554, 556, or 557 of title 5 of the United States Code and which provides for the following:

(1) The presiding officer in the hearing shall be designated by the Secretary from officers and employees of the Department who have not participated in any action of the Secretary which is the subject of the hearing and who are not directly responsible to an officer or employee of the Department who has participated in any such action.

(2) Each party to the hearing shall have the right at all times to be advised and accompanied by an attorney.

(3) Before the hearing, each party to the hearing shall be given reasonable notice of the matters to be considered at the hearing, including a comprehensive statement of the basis for the action taken or proposed by the Secretary which is the subject of the hearing and a general summary of the information which will be presented by the Secretary at the hearing in support of such action.

(4) At the hearing the parties to the hearing shall have the right to hear a full and complete statement of the action of the Secretary which is the subject of the hearing together with the information and reasons supporting such action, to conduct reasonable questioning, and to present any oral or written information relevant to such action.

(5) The presiding officer in such hearing shall prepare a written report of the hearing to which shall be attached all written material presented at the hearing. The participants in the hearing shall be given the opportunity to review and correct or supplement the presiding officer's report of the hearing.
(6) The Secretary may require the hearing to be transcribed. A party to the hearing shall have the right to have the hearing transcribed at his expense. Any transcription of a hearing shall be included in the presiding officer's report of the hearing.

(y) The term "saccharin" includes calcium saccharin, sodium saccharin, and ammonium saccharin.

(z) The term "infant formula" means a food which purports to be or is represented for special dietary use solely as a food for infants by reason of its simulation of human milk or its suitability as a complete or partial substitute for human milk.

(aa) The term "abbreviated drug application" means an application submitted under section 505(j) for the approval of a drug that relies on the approved application of another drug with the same active ingredient to establish safety and efficacy, and -

(1) in the case of section 306, includes a supplement to such an application for a different or additional use of the drug but does not include a supplement to such an application for other than a different or additional use of the drug, and

(2) in the case of sections 307 and 308, includes any supplement to such an application.

(bb) The term "knowingly" or "knew" means that a person, with respect to information -

(1) has actual knowledge of the information, or

(2) acts in deliberate ignorance or reckless disregard of the truth or falsity of the information.

(cc) For purposes of section 306, the term "high managerial agent" -

(1) means -

(A) an officer or director of a corporation or an association,

(B) a partner of a partnership, or

(C) any employee or other agent of a corporation, association, or partnership, having duties such that the conduct of such officer, director, partner, employee, or agent may fairly be assumed to represent the policy of the corporation, association, or partnership, and

(2) includes persons having management responsibility for -

(A) submissions to the Food and Drug Administration regarding the development or approval of any drug product,

(B) production, quality assurance, or quality control of any drug product, or

(C) research and development of any drug product.

(dd) For purposes of sections 306 and 307, the term "drug product" means a drug subject to regulation under section 505, 512, or 802 of this Act or under section 351 of the Public Health Service Act.

(ee) The term "Commissioner" means the Commissioner of Food and Drugs.

(ff) The term "dietary supplement" -

(1) means a product (other than tobacco) intended to supplement the diet that bears or contains one or more of the following dietary ingredients:

(A) a vitamin;

(B) a mineral;

(C) an herb or other botanical;

(D) an amino acid;
(E) a dietary substance for use by man to supplement the diet by increasing the total dietary intake; or

(F) a concentrate, metabolite, constituent, extract, or combination of any ingredient described in clause (A), (B), (C), (D), or (E);

(2) means a product that -

(A)

(i) is intended for ingestion in a form described in section 411(c)(1)(B)(i) of this title; or

(ii) complies with section 411(c)(1)(B)(ii) of this title;

(B) is not represented for use as a conventional food or as a sole item of a meal or the diet; and

(C) is labeled as a dietary supplement; and

(3) does -

(A) include an article that is approved as a new drug under section 505 or licensed as a biologic under section 351 of the Public Health Service Act (42 USC 262) and was, prior to such approval, certification, or license, marketed as a dietary supplement or as a food unless the Secretary has issued a regulation, after notice and comment, finding that the article, when used as or in a dietary supplement under the conditions of use and dosages set forth in the labeling for such dietary supplement, is unlawful under section 402(f) of this title; and

(B) not include -

(i) an article that is approved as a new drug under section 505 of this title, certified as an antibiotic under section 507, or licensed as a biologic under section 351 of the Public Health Service Act (42 USC 262), or

(ii) an article authorized for investigation as a new drug, antibiotic, or biological for which substantial clinical investigations have been instituted and for which the existence of such investigations has been made public, which was not before such approval, certification, licensing, or authorization marketed as a dietary supplement or as a food unless the Secretary, in the Secretary's discretion, has issued a regulation, after notice and comment, finding that the article would be lawful under this chapter.

(gg) The term "processed food" means any food other than a raw agricultural commodity and includes any raw agricultural commodity that has been subject to processing, such as canning, cooking, freezing, dehydration, or milling.

(hh) The term "Administrator" means the Administrator of the United States Environmental Protection Agency.

(ii) The term "compounded positron emission tomography drug-

(1) means a drug that

(A) exhibits spontaneous disintegration of unstable nuclei by the emission of positrons and is used for the purpose of providing dual photon positron emission tomographic diagnostic images; and

(B) has been compounded by or on the order of a practitioner who is licensed by a State to compound or order compounding for a drug described in subparagraph (A), and is compounded in accordance with that State's law, for a patient or for research, teaching, or quality control; and
(2) includes any nonradioactive reagent, reagent kit, ingredient, nuclide generator, accelerator, target material, electronic synthesizer, or other apparatus or computer program to be used in the preparation of such a drug.

(jj) The term "antibiotic drug" means any drug (except drugs for use in animals other than humans) composed wholly or partly of any kind of penicillin, streptomycin, chlortetracycline, chloramphenicol, bacitracin, or any other drug intended for human use containing any quantity of any chemical substance which is produced by a micro-organism and which has the capacity to inhibit or destroy micro-organisms in dilute solution (including a chemically synthesized equivalent of any such substance) or any derivative thereof.

SEC. 301. [331] The following acts and the causing thereof are hereby prohibited:

(a) The introduction or delivery for introduction into interstate commerce of any food, drug, device, or cosmetic that is adulterated or misbranded.

(b) The adulteration or misbranding of any food, drug, device, or cosmetic in interstate commerce.

(c) The receipt in interstate commerce of any food, drug, device, or cosmetic that is adulterated or misbranded, and the delivery or proffered delivery thereof for pay or otherwise.

(d) The introduction or delivery for introduction into interstate commerce of any article in violation of section 404 or 505.

(e) The refusal to permit access to or copying of any record as required by section 412 or 703; or the failure to establish or maintain any record, or make any report, required under section 412, 505(i) or (k), 512(a)(4)(C), 512(j), (l), or (m), 515(f), or 519, or the refusal to permit access to or verification or copying of any such required record.

(f) The refusal to permit entry or inspection as authorized by section 704.

(g) The manufacture within any Territory of any food, drug, device, or cosmetic that is adulterated or misbranded.

(h) The giving of a guaranty or undertaking referred to in section 333(c)(2) of this title, which guaranty or undertaking is false, except by a person who relied upon a guaranty or undertaking to the same effect signed by, and containing the name and address of, the person residing in the United States from whom he received in good faith the food, drug, device, or cosmetic; or the giving of a guaranty or undertaking referred to in section 333(c)(3) of this title, which guaranty or undertaking is false.

(i) Forging, counterfeiting, simulating, or falsely representing, or without proper authority using any mark, stamp, tag, label, or other identification device authorized or required by regulations promulgated under the provisions of section 404, or 721.

(2) Making, selling, disposing of, or keeping in possession, control, or custody, or concealing any punch, die, plate, stone, or other thing designed to print, imprint, or reproduce the trademark, trade name, or other identifying mark, imprint, or device of another or any likeness of any of the foregoing upon any drug or container or labeling thereof so as to render such drug a counterfeit drug.
(3) The doing of any act which causes a drug to be a counterfeit drug, or the sale or dispensing, or the holding for sale or dispensing, of a counterfeit drug.

(j) The using by any person to his own advantage, or revealing, other than to the Secretary or officers or employees of the Department, or to the courts when relevant in any judicial proceeding under this Act, any information acquired under authority of section 404, 409, 412, 505, 510, 512, 513, 514, 515, 516, 518, 519, 520, 704, 708, or 721 concerning any method or process which as a trade secret is entitled to protection, or the violating of section 408(i)(2) or any regulation issued under that section. This paragraph does not authorize the withholding of information from either House of Congress or from, to the extent of matter within its jurisdiction, any committee or subcommittee of such committee or any joint committee of Congress or any subcommittee of such joint committee.

(k) The alteration, mutilation, destruction, obliteration, or removal of the whole or any part of the labeling of, or the doing of any other act with respect to, a food, drug, device, or cosmetic, if such act is done while such article is held for sale (whether or not the first sale) after shipment in interstate commerce and results in such article being adulterated or misbranded.

[(l) Repealed by Pub. L. 105-115, November 21, 1997.]

(m) The sale or offering for sale of colored oleomargarine or colored margarine, or the possession or serving of colored oleomargarine or colored margarine in violation of section 407(b) or 407(c).

(n) The using, in labeling, advertising or other sales promotion of any reference to any report or analysis furnished in compliance with section 704.

(o) In the case of a prescription drug distributed or offered for sale in interstate commerce, the failure of the manufacturer, packer, or distributor thereof to maintain for transmittal, or to transmit, to any practitioner licensed by applicable State law to administer such drug who makes written request for information as to such drug, true and correct copies of all printed matter which is required to be included in any package in which that drug is distributed or sold, or such other printed matter as is approved by the Secretary. Nothing in this paragraph shall be construed to exempt any person from any labeling requirement imposed by or under other provisions of this Act.

(p) The failure to register in accordance with section 510, the failure to provide any information required by section 510(j) or 510(k), or the failure to provide a notice required by section 510(j)(2).

(q)

(1) The failure or refusal to (A) comply with any requirement prescribed under section 518 or 520(g), (B) furnish any notification or other material or information required by or under section 519 or 520(g), or (C) comply with a requirement under section 522.

(2) With respect to any device, the submission of any report that is required by or under this Act that is false or misleading in any material respect.

(r) The movement of a device in violation of an order under section 304(g) or the removal or alteration of any mark or label required by the order to identify the device as detained.
(s) The failure to provide the notice required by section 412(c) or 412(e), the failure to
make the reports required by section 412(f)(1)(B), the failure to retain the records
required by section 412(b)(4), or the failure to meet the requirements prescribed
under section 412(f)(3).
(t) The importation of a drug in violation of section 801(d)(1), the sale, purchase, or trade
of a drug or drug sample or the offer to sell, purchase, or trade a drug or drug sample
in violation of section 503(c), the sale, purchase, or trade of a coupon, the offer to
sell, purchase, or trade such a coupon, or the counterfeiting of such a coupon in
violation of section 503(c)(2), the distribution of a drug sample in violation of section
503(d) or the failure to otherwise comply with the requirements of section 503(d), or
the distribution of drugs in violation of section 503(e) or the failure to otherwise
comply with the requirements of section 503(e).
(u)¹ The failure to comply with any requirements of the provisions of, or any regulations
or orders of the Secretary, under section 512(a)(4)(A), 512(a)(4)(D), or 512(a)(5).
(v) The introduction or delivery for introduction into interstate commerce of a dietary
supplement that is unsafe under section 413.
(w) The making of a knowingly false statement in any record or report required or
requested under subparagraph (A) or (B) of section 801(d)(3), the failure to submit or
maintain records as required by sections 801(d)(3)(A) and 801(d)(3)(B), the release
into interstate commerce of any article imported into the United States under section
801(d)(3) or any finished product made from such article (except for export in
accordance with section 801(e) or 802 or section 351(h) of the Public Health Service
Act), or the failure to export or destroy any component, part or accessory not
incorporated into a drug, biological product or device that will be exported in
accordance with section 801(e) or 802 or section 351(h) of the Public Health Service
Act.
(x) The falsification of a declaration of conformity submitted under section 514(c) or the
failure or refusal to provide data or information requested by the Secretary under
paragraph (3) of such section.
(y) In the case of a drug, device, or food --
(1) the submission of a report or recommendation by a person accredited under
section 523 that is false or misleading in any material respect;
(2) the disclosure by a person accredited under section 523 of confidential
commercial information or any trade secret without the express written consent
of the person who submitted such information or secret to such person; or
(3) the receipt by a person accredited under section 523 of a bribe in any form or the
doing of any corrupt act by such person associated with a responsibility
delegated to such person under this Act.

CHAPTER V - DRUGS AND DEVICES

SEC. 505(i). [355] CHAPTER V - DRUGS AND DEVICES SUBCHAPTER
A - DRUGS AND DEVICES – ADULTERATED DRUGS AND DEVICES –
NEW DRUGS
(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, or 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; and

(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).

(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 the date of the enactment of the Food and Drug Administration Modernization Act of 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.

SEC. 520(g). [360j] GENERAL PROVISIONS RESPECTING CONTROL OF DEVICES INTENDED FOR HUMAN USE – General Rule – Exemption for Devices for Investigational Use

(1) It is the purpose of this subsection to encourage, to the extent consistent with the protection of the public health and safety and with ethical standards, the discovery and development of useful devices intended for human use and to that end to maintain optimum freedom for scientific investigators in their pursuit of that purpose.

(2) (A) The Secretary shall, within the one hundred and twenty-day period beginning on the date of enactment of this section, by regulation prescribe procedures and conditions under which devices intended for human use may upon application be granted an exemption from the requirements of section 502, 510, 514, 515, 516, 519, or 721 or subsection (e) or (f) of this section or from any combination of such requirements to permit the investigational use of such devices by experts qualified by scientific training and experience to investigate the safety and effectiveness of such devices.

(B) The conditions prescribed pursuant to subparagraph (A) shall include the following:

(i) A requirement that an application be submitted to the Secretary before an exemption may be granted and that the application be submitted in such form and manner as the Secretary shall specify.

(ii) A requirement that the person applying for an exemption for a device assure the establishment and maintenance of such records, and the making of such reports to the Secretary of data obtained as a result of the investigational use of the device during the exemption, as the Secretary determines will enable him to assure compliance with such conditions, review the progress of the investigation, and evaluate the safety and effectiveness of the device.
(iii) Such other requirements as the Secretary may determine to be necessary for the protection of the public health and safety.

(C) Procedures and conditions prescribed pursuant to subparagraph (A) for an exemption may appropriately vary depending on (i) the scope and duration of clinical testing to be conducted under such exemption, (ii) the number of human subjects that are to be involved in such testing, (iii) the need to permit changes to be made in the device subject to the exemption during testing conducted in accordance with a clinical testing plan required under paragraph (3)(A), and (iv) whether the clinical testing of such device is for the purpose of developing data to obtain approval for the commercial distribution of such device.

(3) Procedures and conditions prescribed pursuant to paragraph (2)(A) shall require, as a condition to the exemption of any device to be the subject of testing involving human subjects, that the person applying for the exemption --

(A) submit a plan for any proposed clinical testing of the device and a report of prior investigations of the device (including, where appropriate, tests on animals) adequate to justify the proposed clinical testing --

(i) to the local institutional review committee which has been established in accordance with regulations of the Secretary to supervise clinical testing of devices in the facilities where the proposed clinical testing is to be conducted, or

(ii) to the Secretary, if --

(I) no such committee exists, or

(II) the Secretary finds that the process of review by such committee is inadequate (whether or not the plan for such testing has been approved by such committee), for review for adequacy to justify the commencement of such testing; and, unless the plan and report are submitted to the Secretary, submit to the Secretary a summary of the plan and a report of prior investigations of the device (including, where appropriate, tests on animals);

(B) promptly notify the Secretary (under such circumstances and in such manner as the Secretary prescribes) of approval by a local institutional review committee of any clinical testing plan submitted to it in accordance with subparagraph (A);

(C) in the case of a device to be distributed to investigators for testing, obtain signed agreements from each of such investigators that any testing of the device involving human subjects will be under such investigator's supervision and in accordance with subparagraph (D) and submit such agreements to the Secretary; and

(D) assure that informed consent will be obtained from each human subject (or his representative) of proposed clinical testing involving such device, except where subject to such conditions as the Secretary may prescribe, the investigator conducting or supervising the proposed clinical testing of the device determines in writing that there exists a life threatening situation involving the human subject of such testing which necessitates the use of such device and it is not feasible to obtain informed consent from the subject and there is not sufficient time to obtain such consent from his representative. The determination required by subparagraph (D) shall be concurred in by a licensed physician who is not
involved in the testing of the human subject with respect to which such
determination is made unless immediate use of the device is required to save the
life of the human subject of such testing and there is not sufficient time to obtain
such concurrence.

(4)

(A) An application, submitted in accordance with the procedures prescribed by
regulations under paragraph (2), for an exemption for a device (other than an
exemption from section 516) shall be deemed approved on the thirtieth day after
the submission of the application to the Secretary unless on or before such day
the Secretary by order disapproves the application and notifies the applicant of
the disapproval of the application.

(B) The Secretary may disapprove an application only if he finds that the
investigation with respect to which the application is submitted does not
conform to procedures and conditions prescribed under regulations under
paragraph (2). Such a notification shall contain the order of disapproval and a
complete statement of the reasons for the Secretary's disapproval of the
application and afford the applicant opportunity for an informal hearing on the
disapproval order.

(5) The Secretary may by order withdraw an exemption granted under this subsection for
a device if the Secretary determines that the conditions applicable to the device under
this subsection for such exemption are not met. Such an order may be issued only
after opportunity for an informal hearing, except that such an order may be issued
before the provision of an opportunity for an informal hearing if the Secretary
determines that the continuation of testing under the exemption with respect to which
the order is to be issued will result in an unreasonable risk to the public health.

(6)

(A) Not later than 1 year after the date of the enactment of the Food and Drug
Administration Modernization Act of 1997, the Secretary shall by regulation
establish, with respect to a device for which an exemption under this subsection
is in effect, procedures and conditions that, without requiring an additional
approval of an application for an exemption or the approval of a supplement to
such an application, permit --

(i) developmental changes in the device (including manufacturing changes) that
do not constitute a significant change in design or in basic principles of
operation and that are made in response to information gathered during the
course of an investigation; and

(ii) changes or modifications to clinical protocols that do not affect --

(I) the validity of data or information resulting from the completion of an
approved protocol, or the relationship of likely patient risk to benefit
relied upon to approve a protocol;

(II) the scientific soundness of an investigational plan submitted under
paragraph (3)(A); or

(III) the rights, safety, or welfare of the human subjects involved in the
investigation.

(B) Regulations under subparagraph (A) shall provide that a change or modification
described in such subparagraph may be made if --
(i) the sponsor of the investigation determines, on the basis of credible information (as defined by the Secretary) that the applicable conditions under subparagraph (A) are met; and
(ii) the sponsor submits to the Secretary, not later than 5 days after making the change or modification, a notice of the change or modification.

(7)

(A) In the case of a person intending to investigate the safety or effectiveness of a class III device or any implantable device, the Secretary shall ensure that the person has an opportunity, prior to submitting an application to the Secretary or to an institutional review committee, to submit to the Secretary, for review, an investigational plan (including a clinical protocol). If the applicant submits a written request for a meeting with the Secretary regarding such review, the Secretary shall, not later than 30 days after receiving the request, meet with the applicant for the purpose of reaching agreement regarding the investigational plan (including a clinical protocol). The written request shall include a detailed description of the device, a detailed description of the proposed conditions of use of the device, a proposed plan (including a clinical protocol) for determining whether there is a reasonable assurance of effectiveness, and, if available information regarding the expected performance from the device.

(B) Any agreement regarding the parameters of an investigational plan (including a clinical protocol) 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. Any such agreement shall not be changed, except --

(i) with the written agreement of the sponsor or applicant; or
(ii) pursuant to a decision, made in accordance with subparagraph (C) by the director of the office in which the device involved is reviewed, that a substantial scientific issue essential to determining the safety or effectiveness of the device involved has been identified.

(C) A decision under subparagraph (B)(ii) by the director shall be in writing, and may be made only after the Secretary has provided to the sponsor or applicant an opportunity for a meeting at which the director and the sponsor or applicant are present and at which the director documents the scientific issue involved.

CHAPTER IX - MISCELLANEOUS

SEC. 906 PRACTICE OF MEDICINE. --

Nothing in this Act shall be construed to limit or interfere with the authority of a health care practitioner to prescribe or administer any legally marketed device to a patient for any condition or disease within a legitimate health care practitioner-patient relationship. This section shall not limit any existing authority of the Secretary to establish and enforce restrictions on the sale or distribution, or in the labeling, of a device that are part of a determination of substantial equivalence, established as a condition of approval, or promulgated through regulations. Further, this section shall not change any existing prohibition on the promotion of unapproved uses of legally marketed devices.