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TITLE 21--FOOD AND DRUGS
CHAPTER I--FOOD AND DRUG ADMINISTRATION
DEPARTMENT OF HEALTH AND HUMAN SERVICES
SUBCHAPTER F--BIOLOGICS
PART 601LICENSING

Subpart A--General Provisions

Sec. 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 or the Director, Center for Drug Evaluation and Research (see mailing addresses in 600.2 of this chapter), 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 by the Food and Drug Administration. 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. 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) [Reserved]

(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, 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. 201et 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, as amended at 70 FR 14983, Mar. 24, 2005]

Sec. 601.3 Complete response letter to the applicant.

(a)*Complete response letter* . The Food and Drug Administration will send the biologics license applicant or supplement applicant a complete response letter if the agency determines that it will not approve the biologics license application or supplement in its present form.

(1)*Description of specific deficiencies* . A complete response letter will describe all of the deficiencies that the agency has identified in a biologics license application or supplement, except as stated in paragraph (a)(2) of this section.

(2)*Inadequate data* . If FDA determines, after a biologics license application or supplement is filed, that the data submitted are inadequate to support approval, the agency might issue a complete response letter without first conducting required inspections, testing submitted product lots, and/or reviewing proposed product labeling.

(3)*Recommendation of actions for approval* . When possible, a complete response letter will recommend actions that the applicant might take to place its biologics license application or supplement in condition for approval.

(b)*Applicant actions* . After receiving a complete response letter, the biologics license applicant or supplement applicant must take either of the following actions:

(1)*Resubmission* . Resubmit the application or supplement, addressing all deficiencies identified in the complete response letter.

(2)*Withdrawal* . Withdraw the application or supplement. A decision to withdraw the application or supplement is without prejudice to a subsequent submission.

(c)*Failure to take action* . (1) FDA may consider a biologics license applicant or supplement applicant's failure to either resubmit or withdraw the application or supplement within 1 year after issuance of a complete response letter to be a request by the applicant to withdraw the application or supplement, unless the applicant has requested an extension of time in which to resubmit the application or supplement. FDA will grant any reasonable request for such an extension. FDA may consider an applicant's failure to resubmit the application or supplement within the extended time period or request an additional extension to be a request by the applicant to withdraw the application.

(2) If FDA considers an applicant's failure to take action in accordance with paragraph (c)(1) of this section to be a request to withdraw the application, the agency will notify the applicant in writing. The applicant will have 30 days from the date of the notification to explain why the application or supplement should not be withdrawn and to request an extension of time in which to resubmit the application or supplement. FDA will grant any reasonable request for an extension. If the applicant does not respond to the notification within 30 days, the application or supplement will be deemed to be withdrawn.

[73 FR 39611, July 10, 2008]

Sec. 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 or the Director, Center for Drug 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.

[42 FR 4718, Jan. 25, 1977, as amended at 42 FR 15676, Mar. 22, 1977; 42 FR 19142, Apr. 12, 1977; 64 FR 56450, Oct. 20, 1999; 70 FR 14983, Mar. 24, 2005]

Sec. 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.

[64 FR 56451, Oct. 20, 1999]

Sec. 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 Center for Biologics Evaluation and Research or the Center for Drug 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.

[64 FR 56451, Oct. 20, 1999, as amended at 70 FR 14983, Mar. 24, 2005]

Sec. 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.

[42 FR 4718, Jan. 25, 1977, as amended at 42 FR 15676, Mar. 22, 1977; 42 FR 19143, Apr. 12, 1977]

Sec. 601.8 Publication of revocation.

The Commissioner, following revocation of a biologics license under 21 CFR 601.5(b), will publish a notice in the Federal Register with a statement of the specific grounds for the revocation.

[74 FR 20585, May 5, 2009]

Sec. 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 or the Director, Center for Drug 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, as amended at 70 FR 14983, Mar. 24, 2005]

Subpart B [Reserved]

Subpart C--Biologics Licensing

Sec. 601.12 Changes to an approved application.

(a) *General* . (1) As provided by this section, an applicant must inform the Food and Drug Administration (FDA) (see mailing addresses in 600.2 of this chapter) about each change in the product, production process, quality controls, equipment, facilities, responsible personnel, or labeling established in the approved license application(s).

(2) Before distributing a product made using a change, an applicant must assess the effects of the change and demonstrate through appropriate validation and/or other clinical and/or nonclinical 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.

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

(4) The applicant must promptly revise all promotional labeling and advertising to make it consistent with any labeling change implemented in accordance with paragraphs (f)(1) and (f)(2) of this section.

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

(b) *Changes requiring supplement submission and approval prior to distribution of the product made using the change (major changes)*. (1) A supplement shall be submitted for any change in the product, production process, quality controls, equipment, facilities, or responsible personnel 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.

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

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

(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).

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

(c) *Changes requiring supplement submission at least 30 days prior to distribution of the 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 Effectuated in 30 Days" or, if applicable under paragraph (c)(5) of this section, "Supplement--Changes Being Effectuated."

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

(i) [Reserved]

(ii) An increase or decrease in production scale during finishing steps that involves 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.

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

(3) 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 Effectuated" 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 (e) of this section.

(6) If the agency disapproves the supplemental application, it may order the manufacturer to cease distribution of the products made with the manufacturing change.

(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 or the Director, Center for Drug 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 a change to an official compendium, except a change described in paragraph (c)(2)(iv) of this section, that is consistent with FDA statutory and regulatory requirements.

(ii) The deletion or reduction 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 dating period based upon full shelf life data on production batches obtained from a protocol approved in the application;

(iv) A change within the container closure system for a nonsterile product, 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 and/or shape of a container containing the same number of dosage units for a nonsterile solid dosage form product, without a change from one container 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 revision of an alternative analytical procedure that provides the same or increased assurance of the identity, strength, quality, purity, or potency of the material being tested as the analytical procedure described in the approved application, or deletion of an alternative analytical procedure.

(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.

(iii) A statement by the holder of the approved application or license that the effects of the change have been assessed.

(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. An applicant cannot use paragraph (f)(2) of this section to make any change to the information required in 201.57(a) of this chapter. An applicant may report the minor

changes to the information specified in paragraph (f)(3)(i)(D) of this section in an annual report. 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 reflect newly acquired information, except for changes to the package insert required in 201.57(a) of this chapter (which must be made under paragraph (f)(1) of this section), to accomplish any of the following:

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

(B) To add or strengthen a statement about 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.

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

(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, container 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;

(C) A change in the information specified in 208.20(b)(8)(iii) and (b)(8)(iv) of this chapter for a Medication Guide; and

(D) A change to the information required in 201.57(a) of this chapter as follows:

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

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

(E) A change made pursuant to an exception or alternative granted under 201.26 or 610.68 of this chapter.

(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 or Center for Drug 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.

(5) The submission and grant of a written request for an exception or alternative under 201.26 or 610.68 of this chapter satisfies the requirements in paragraphs (f)(1) through (f)(2) of this section.

(6) For purposes of paragraph (f)(2) of this section, information will be

considered newly acquired if it consists of data, analyses, or other information not previously submitted to the agency, which may include (but are not limited to) data derived from new clinical studies, reports of adverse events, or new analyses of previously submitted data (e.g., meta-analyses) if the studies, events or analyses reveal risks of a different type or greater severity or frequency than previously included in submissions to FDA.

(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.

[62 FR 39901, July 24, 1997, as amended at 63 FR 66399, Dec. 1, 1998. Redesignated at 65 FR 59718, Oct. 6, 2000, and amended at 69 FR 18766, Apr. 8, 2004; 70 FR 14983, Mar. 24, 2005; 71 FR 3997, Jan. 24, 2006; 72 FR 73600, Dec. 28, 2007; 73 FR 49609, Aug. 22, 2008; 73 FR 68333, Nov. 18, 2008]

Sec. 601.14 Regulatory submissions in electronic format.

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

(b)*Labeling.* The content of labeling required under 201.100(d)(3) of this chapter (commonly referred to as the package insert or professional labeling), including all text, tables, and figures, must be submitted to the agency in electronic format as described in paragraph (a) of this section. This requirement is in addition to the provisions of 601.2(a) and 601.12(f) that require applicants to submit specimens of the labels, enclosures, and containers, or to submit other final printed labeling. Submissions under this paragraph must be made in accordance with part 11 of this chapter except for the requirements of 11.10(a), (c) through (h), and (k), and the corresponding requirements of 11.30.

[68 FR 69020, Dec. 11, 2003]

Sec. 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 or the Director, Center for Drug Evaluation and Research (see mailing addresses in 600.2 of this chapter) must be at least two final containers of each lot of product. A copy of the associated documents which describe and identify the shipment must accompany the shipment for forwarding with the samples to the Director, Center for Biologics Evaluation and Research or the Director, Center for Drug Evaluation and Research (see mailing addresses in 600.2). 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 or Center for Drug Evaluation and Research accompanies each shipment.

[70 FR 14983, Mar. 24, 2005]

Sec. 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 or the Director, Center for Drug 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, as amended at 70 FR 14983, Mar. 24, 2005]

Sec. 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]

Sec. 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.

[42 FR 4718, Jan. 25, 1977, as amended at 61 FR 24233, May 14, 1996; 64 FR 56452, Oct. 20, 1999]

Sec. 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 Division of Dockets Management 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* 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 rationale 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.²

(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.²

(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 Division of Dockets Management 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.

²As 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.

[38 FR 32052, Nov. 20, 1973, as amended at 39 FR 11535, Mar. 29, 1974; 40 FR 13498, Mar. 27, 1975; 43 FR 44838, Sept. 29, 1978; 47 FR 44071, Oct. 5, 1982; 47 FR 50211, Nov. 5, 1982; 51 FR 15607, Apr. 25, 1986; 55 FR 11014, Mar. 26, 1990; 62 FR 53538, Oct. 15, 1997; 64 FR 56452, Oct. 20, 1999]

Sec. 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:

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).

(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.

[47 FR 44071, Oct. 5, 1982, as amended at 64 FR 56452, Oct. 20, 1999]

Sec. 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]

Sec. 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 each product under the license to the Director, Center for Biologics Evaluation and Research or the Director, Center for Drug Evaluation and Research (see mailing addresses in 600.2 of this chapter):

(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.

[65 FR 59718, Oct. 6, 2000, as amended at 65 FR 64618, Oct. 30, 2000; 70 FR 14984, Mar. 24, 2005]

Sec. 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 (see mailing addresses in 600.2 of this chapter).

[65 FR 56480, Sept. 19, 2000, as amended at 70 FR 14984, Mar. 24, 2005]

Subpart D--Diagnostic Radiopharmaceuticals

Sec. 601.30 Scope.

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.

Sec. 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.

Sec. 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.

Sec. 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.

Sec. 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.

Sec. 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)(1) 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 in humans and appropriate animal models. The maximum tolerated dose need not be established.

Subpart E--Accelerated Approval of Biological Products for Serious or Life-Threatening Illnesses

Sec. 601.40 Scope.

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).

Sec. 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.

Sec. 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.

Sec. 601.43 Withdrawal procedures.

(a) For biological products approved under 601.41 or 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 or 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 601.41 or 601.42. 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 58959, Dec. 11, 1992, as amended at 68 FR 34797, June 11, 2003; 70 FR 14984, Mar. 24, 2005]

Sec. 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.

Sec. 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.

Sec. 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

Sec. 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]

Sec. 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 Food and Drug Administration 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)(1) 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 Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852, 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.

[39 FR 44656, Dec. 24, 1974, as amended at 42 FR 15676, Mar. 22, 1977; 49 FR 23833, June 8, 1984; 55 FR 11013, Mar. 26, 1990; 61 FR 51530, Oct. 2, 1996; 64 FR 56452, Oct. 20, 1999; 68 FR 24879, May 9, 2003; 69 FR 13717, Mar. 24, 2004; 70 FR 14984, Mar. 24, 2005]

Subpart G--Postmarketing Studies

Sec. 601.70 Annual progress reports of postmarketing studies.

(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, 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)(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 Center for Biologics Evaluation and Research or Center for Drug Evaluation and Research (see mailing addresses in 600.2 of this chapter).

(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.

[65 FR 64618, Oct. 30, 2000, as amended at 70 FR 14984, Mar. 24, 2005]

Subpart H--Approval of Biological Products When Human Efficacy Studies Are Not Ethical or Feasible

Sec. 601.90 Scope.

This subpart applies to certain biological products that have been studied for their safety and efficacy in ameliorating or preventing serious or life-threatening conditions caused by exposure to lethal or permanently disabling toxic biological, chemical, radiological, or nuclear substances. This subpart applies only to those biological products for which: Definitive human efficacy studies cannot be conducted because it would be unethical to deliberately expose healthy human volunteers to a lethal or permanently disabling toxic biological, chemical, radiological, or nuclear substance; and field trials to study the product's efficacy after an accidental or hostile exposure have not been feasible. This subpart does not apply to products that can be approved

based on efficacy standards described elsewhere in FDA's regulations (e.g., accelerated approval based on surrogate markers or clinical endpoints other than survival or irreversible morbidity), nor does it address the safety evaluation for the products to which it does apply.

Sec. 601.91 Approval based on evidence of effectiveness from studies in animals.

(a) FDA may grant marketing approval for a biological product for which safety has been established and for which the requirements of 601.90 are met based on adequate and well-controlled animal studies when the results of those animal studies establish that the biological product is reasonably likely to produce clinical benefit in humans. In assessing the sufficiency of animal data, the agency may take into account other data, including human data, available to the agency. FDA will rely on the evidence from studies in animals to provide substantial evidence of the effectiveness of these products only when:

(1) There is a reasonably well-understood pathophysiological mechanism of the toxicity of the substance and its prevention or substantial reduction by the product;

(2) The effect is demonstrated in more than one animal species expected to react with a response predictive for humans, unless the effect is demonstrated in a single animal species that represents a sufficiently well-characterized animal model for predicting the response in humans;

(3) The animal study endpoint is clearly related to the desired benefit in humans, generally the enhancement of survival or prevention of major morbidity; and

(4) The data or information on the kinetics and pharmacodynamics of the product or other relevant data or information, in animals and humans, allows selection of an effective dose in humans.

(b) Approval under this subpart will be subject to three requirements:

(1) *Postmarketing studies.* The applicant must conduct postmarketing studies, such as field studies, to verify and describe the biological product's clinical benefit and to assess its safety when used as indicated when such studies are feasible and ethical. Such postmarketing studies would not be feasible until an exigency arises. When such studies are feasible, the applicant must conduct such studies with due diligence. Applicants must include as part of their application a plan or approach to postmarketing study commitments in the event such studies become ethical and feasible.

(2) *Approval with restrictions to ensure safe use.* If FDA concludes that a biological product shown to be effective under this subpart can be safely used only if distribution or use is restricted, FDA will require such postmarketing restrictions as are needed to ensure safe use of the biological product, commensurate with the specific safety concerns presented by the biological product, such as:

(i) Distribution restricted to certain facilities or health care practitioners with special training or experience;

(ii) Distribution conditioned on the performance of specified medical procedures, including medical followup; and

(iii) Distribution conditioned on specified recordkeeping requirements.

(3) *Information to be provided to patient recipients.* For biological products or specific indications approved under this subpart, applicants must prepare, as part of their proposed labeling, labeling to be provided to patient recipients. The patient labeling must explain that, for ethical or feasibility reasons, the biological product's approval was based on efficacy studies conducted in animals alone and must give the biological product's indication (s), directions for use (dosage and administration), contraindications, a description of any reasonably foreseeable risks, adverse reactions, anticipated benefits, drug interactions, and any other relevant information required by FDA at the time of approval. The patient labeling must be available with the product to be provided to patients prior to administration or dispensing of the biological product for the use approved under this subpart, if possible.

Sec. 601.92 Withdrawal procedures.

(a)*Reasons to withdraw approval.* For biological products approved under this subpart, 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 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 applied at the time of approval under this subpart;
- (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 or the Director of the Center for Drug Evaluation and Research will give the applicant notice of an opportunity for a hearing on the proposal to withdraw the approval of an application approved under this subpart. 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 CBER 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 of Food and Drugs' 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.

[67 FR 37996, May 31, 2002, as amended at 70 FR 14984, Mar. 24, 2005]

Sec. 601.93 Postmarketing safety reporting.

Biological products approved under this subpart are subject to the postmarketing recordkeeping and safety reporting applicable to all approved biological products.

Sec. 601.94 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.

Sec. 601.95 Termination of requirements.

If FDA determines after approval under this subpart that the requirements established in 601.91(b)(2), 601.92, and 601.93 are no longer necessary for the safe and effective use of a biological product, FDA will so notify the applicant. Ordinarily, for biological products approved under 601.91, these requirements will no longer apply when FDA determines that the postmarketing study verifies and describes the biological product's clinical benefit. For biological products approved under 601.91, the restrictions would no longer apply when FDA determines that safe use of the biological product can be ensured 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 of this chapter.

Authority: 15 U.S.C. 1451-1561; 21 U.S.C. 321, 351, 352, 353, 355, 356b, 360, 360c-360f, 360h-360j, 371, 374, 379e, 381; 42 U.S.C. 216, 241, 262, 263, 264; sec 122, Pub. L. 105-115, 111 Stat. 2322 (21 U.S.C. 355 note).

Source: 38 FR 32052, Nov. 20, 1973, unless otherwise noted.

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