SUBCHAPTER F—BIOLOGICS

PART 600—BIOLOGICAL PRODUCTS: GENERAL

Subpart A—General Provisions

Subpart B—Establishment Standards

Subpart C—Establishment Inspection

Subpart D—Reporting of Adverse Experiences

AUTHORITY: 21 U.S.C. 321, 351, 352, 353, 355, 360, 360i, 371, 374; 42 U.S.C. 216, 262, 263, 263a, 264, 300aa–25.

EFFECTIVE DATE NOTE: At 79 FR 33090, June 10, 2014, the authority citation of part 600 was revised, effective June 10, 2015. For the convenience of the user, the revised text is set forth as follows:

AUTHORITY: 21 U.S.C. 321, 351, 352, 353, 355, 360, 360i, 371, 374, 379k–1; 42 U.S.C. 216, 262, 263, 263a, 264, 300aa–25.

CROSS REFERENCES: For U.S. Customs Service regulations relating to viruses, serums, and toxins, see 19 CFR 12.21–12.23. For U.S. Postal Service regulations relating to the admissibility to the United States mails see parts 124 and 125 of the Domestic Mail Manual, that is incorporated by reference in 39 CFR part 111.

Subpart A—General Provisions

§ 600.2 Mailing addresses.

(a) *Licensed biological products regulated by the Center for Biologics Evaluation and Research (CBER).* Unless otherwise stated in paragraphs (c) or (d) of this section, or as otherwise prescribed by FDA regulation, all submissions to CBER referenced in parts 600 through 680 of this chapter, as applicable, must be sent to: Document Control Center (HFM–99), Center for Biologics Evaluation and Research, Food and Drug Administration, 1401 Rockville Pike, suite 200N, Rockville, MD 20852–1448. Examples of such submissions include: Biologics license applications (BLAs) and their amendments and supplements, adverse experience reports, biological product deviation reports, fatality reports, and other correspondence. Biological products samples must not be sent to this address but must be sent to the address in paragraph (c) of this section.

(b) *Licensed biological products regulated by the Center for Drug Evaluation and Research (CDER).* Unless otherwise stated in paragraphs (b)(1), (b)(2), (b)(3), or (c) of this section, or as otherwise prescribed by FDA regulation, all submissions to CDER referenced in parts 600, 601, and 610 of this chapter, as applicable, must be sent to: CDER Central Document Room, Center for Drug Evaluation and Research, Food and Drug Administration, 5901B Ammendale Rd., Beltsville, MD 20705. Examples of such submissions include: BLAs and their amendments and supplements, and other correspondence.

(1) *Biological Product Deviation Reporting (CDER).* All biological product deviation reports required under § 600.14 must be sent to: Division of Compliance Risk Management and Surveillance, Office of Compliance, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Silver Spring, MD 20993–0002.

(2) *Postmarketing Adverse Experience Reporting (CDER).* All postmarketing reports required under § 600.80 must be sent to: Central Document Room, Center for Drug Evaluation and Research, Food and Drug Administration, 5901–B Ammendale Rd., Beltsville, MD 20705–1266.

(3) *Advertising and Promotional Labeling (CDER).* All advertising and promotional labeling supplements required under § 601.12(f) of this chapter must be sent to: Division of Drug Marketing, Advertising and Communication, Center for Drug Evaluation and Research, Food and Drug Administration, 5901–B Ammendale Rd., Beltsville, MD 20705–1266.

(c) *Samples and Protocols for licensed biological products regulated by CBER or CDER.* (1) Biological product samples and/or protocols, other than radioactive biological product samples and protocols, required under §§ 600.13, 600.22, 601.15, 610.2, 660.6, 660.36, or 660.46 of this chapter must be sent by courier service to: Sample Custodian (ATTN: HFM–672), Food and Drug Administration. Center for Biologics Evaluation and Research, Bldg: NLRC–B, rm. 113, 5516 Nicholson Lane, Kensington, MD 20895. The protocol(s) may be placed in the box used to ship the samples to CBER. A cover letter should not be included when submitting the protocol with the sample unless it contains pertinent information affecting the release of the lot.

(2) Radioactive biological products required under § 610.2 of this chapter must be sent by courier service to: Sample Custodian (ATTN: HFM–672), Food and Drug Administration, Center for Biologics Evaluation and Research, Nicholson Lane Research Center, c/o Radiation Safety Office, National Institutes of Health, 21 Wilson Dr., rm. 107, Bethesda, MD 20892–6780.

(d) *Vaccine Adverse Event Reporting System (VAERS).* All VAERS reports as specified in § 600.80(c) must be sent to: Vaccine Adverse Event Reporting System (VAERS), P.O. Box 1100, Rockville, MD 20849–1100.

(e) Address information for submissions to CBER and CDER other than those listed in parts 600 through 680 of this chapter are included directly in the applicable regulations.

(f) Obtain updated mailing address information for biological products regulated by CBER at *http://www.fda.gov/cber/pubinquire.htm,* or for biological products regulated by CDER at *http://www.fda.gov/cder/biologics/default.htm.*

[70 FR 14981, Mar. 24, 2005, as amended at 74 FR 13114, Mar. 26, 2009; 78 FR 19585, Apr. 2, 2013]

EFFECTIVE DATE NOTE: At 79 FR 33090, June 10, 2014, § 600.2 was amended as follows, effective June 10, 2015.

a. In paragraph (a) by removing the phrase "paragraphs (c) or (d)" and adding in its place "paragraph (c)", and by removing the phrase "adverse experience reports";

b. In paragraph (b) introductory text by removing the phrase "paragraphs (b)(1), (b)(2), (b)(3), or (c)" and adding in its place "paragraphs (b)(1), (b)(2), or (c) "

c. By removing paragraph (b)(2) and redesignating paragraph (b)(3) as paragraph (b)(2);

d. By removing paragraph (d) and redesignating paragraphs (e) and (f) as paragraphs (d) and (e).

e. In newly redesignated paragraph (e) by removing the Web address "*http://www.fda.gov/cber/pubinquire.htm*" and adding in its place "*http://www.fda.gov/BiologicsBloodVaccines/default.htm*" and by removing the Web address "*http://www.fda.gov/cder/biologics/default.htm*" and adding in its place "*http://www.fda.gov/Drugs/default.htm*".

§ 600.3 Definitions.

As used in this subchapter:

(a) *Act* means the Public Health Service Act (58 Stat. 682), approved July 1, 1944.

(b) *Secretary* means the Secretary of Health and Human Services and any other officer or employee of the Department of Health and Human Services to whom the authority involved has been delegated.

(c) *Commissioner of Food and Drugs* means the Commissioner of the Food and Drug Administration.

(d) *Center for Biologics Evaluation and Research* means Center for Biologics Evaluation and Research of the Food and Drug Administration.

(e) *State* means a State or the District of Columbia, Puerto Rico, or the Virgin Islands.

(f) *Possession* includes among other possessions, Puerto Rico and the Virgin Islands.

(g) *Products* includes biological products and trivalent organic arsenicals.

(h) *Biological product* means any virus, therapeutic serum, toxin, antitoxin, or analogous product applicable to the prevention, treatment or cure of diseases or injuries of man:

(1) A virus is interpreted to be a product containing the minute living cause of an infectious disease and includes but is not limited to filterable viruses, bacteria, rickettsia, fungi, and protozoa.

(2) A therapeutic serum is a product obtained from blood by removing the clot or clot components and the blood cells.

(3) A toxin is a product containing a soluble substance poisonous to laboratory animals or to man in doses of 1 milliliter or less (or equivalent in weight) of the product, and having the property, following the injection of non-fatal doses into an animal, of causing to be produced therein another soluble substance which specifically neutralizes the poisonous substance and which is demonstrable in the serum of the animal thus immunized.

(4) An antitoxin is a product containing the soluble substance in serum or other body fluid of an immunized animal which specifically neutralizes the toxin against which the animal is immune.

(5) A product is analogous:

(i) To a virus if prepared from or with a virus or agent actually or potentially infectious, without regard to the degree of virulence or toxicogenicity of the specific strain used.

(ii) To a therapeutic serum, if composed of whole blood or plasma or containing some organic constituent or product other than a hormone or an amino acid, derived from whole blood, plasma, or serum.

(iii) To a toxin or antitoxin, if intended, irrespective of its source of origin, to be applicable to the prevention, treatment, or cure of disease or injuries of man through a specific immune process.

(i) *Trivalent organic arsenicals* means arsphenamine and its derivatives (or any other trivalent organic arsenic compound) applicable to the prevention, treatment, or cure of diseases or injuries of man.

(j) A product is deemed *applicable to the prevention, treatment, or cure of diseases or injuries of man* irrespective of the mode of administration or application recommended, including use when intended through administration or application to a person as an aid in diagnosis, or in evaluating the degree of susceptibility or immunity possessed by a person, and including also any other use for purposes of diagnosis if the diagnostic substance so used is prepared from or with the aid of a biological product.

(k) *Proper name*, as applied to a product, means the name designated in the license for use upon each package of the product.

(l) *Dating period* means the period beyond which the product cannot be expected beyond reasonable doubt to yield its specific results.

(m) *Expiration date* means the calendar month and year, and where applicable, the day and hour, that the dating period ends.

(n) The word *standards* means specifications and procedures applicable to an establishment or to the manufacture or release of products, which are prescribed in this subchapter or established in the biologics license application designed to insure the continued safety, purity, and potency of such products.

(o) The word *continued* as applied to the safety, purity and potency of products is interpreted to apply to the dating period.

(p) The word *safety* means the relative freedom from harmful effect to persons affected, directly or indirectly, by a product when prudently administered, taking into consideration the character of the product in relation to the condition of the recipient at the time.

(q) The word *sterility* is interpreted to mean freedom from viable contaminating microorganisms, as determined by the tests conducted under § 610.12 of this chapter.

(r) *Purity* means relative freedom from extraneous matter in the finished product, whether or not harmful to the recipient or deleterious to the product. *Purity* includes but is not limited to relative freedom from residual moisture or other volatile substances and pyrogenic substances.

(s) The word *potency* is interpreted to mean the specific ability or capacity of the product, as indicated by appropriate laboratory tests or by adequately controlled clinical data obtained through the administration of

the product in the manner intended, to effect a given result.

(t) *Manufacturer* means any legal person or entity engaged in the manufacture of a product subject to license under the act; "Manufacturer" also includes any legal person or entity who is an applicant for a license where the applicant assumes responsibility for compliance with the applicable product and establishment standards.

(u) *Manufacture* means all steps in propagation or manufacture and preparation of products and includes but is not limited to filling, testing, labeling, packaging, and storage by the manufacturer.

(v) *Location* includes all buildings, appurtenances, equipment and animals used, and personnel engaged by a manufacturer within a particular area designated by an address adequate for identification.

(w) *Establishment* has the same meaning as "facility" in section 351 of the Public Health Service Act and includes all locations.

(x) *Lot* means that quantity of uniform material identified by the manufacturer as having been thoroughly mixed in a single vessel.

(y) A *filling* refers to a group of final containers identical in all respects, which have been filled with the same product from the same bulk lot without any change that will affect the integrity of the filling assembly.

(z) *Process* refers to a manufacturing step that is performed on the product itself which may affect its safety, purity or potency, in contrast to such manufacturing steps which do not affect intrinsically the safety, purity or potency of the product.

(aa) *Selling agent* or *distributor* means any person engaged in the unrestricted distribution, other than by sale at retail, of products subject to license.

(bb) *Container* (referred to also as "final container") is the immediate unit, bottle, vial, ampule, tube, or other receptacle containing the product as distributed for sale, barter, or exchange.

(cc) *Package* means the immediate carton, receptacle, or wrapper, including all labeling matter therein and thereon, and the contents of the one or more enclosed containers. If no package, as defined in the preceding sentence, is used, the container shall be deemed to be the package.

(dd) *Label* means any written, printed, or graphic matter on the container or package or any such matter clearly visible through the immediate carton, receptacle, or wrapper.

(ee) *Radioactive biological product* means a biological product which is labeled with a radionuclide or intended solely to be labeled with a radionuclide.

(ff) *Amendment* is the submission of information to a pending license application or supplement, to revise or modify the application as originally submitted.

(gg) *Supplement* is a request to approve a change in an approved license application.

(hh) *Distributed* means the biological product has left the control of the licensed manufacturer.

(ii) *Control* means having responsibility for maintaining the continued safety, purity, and potency of the product and for compliance with applicable product and establishment standards, and for compliance with current good manufacturing practices.

(jj) *Assess the effects of the change*, as used in § 601.12 of this chapter, means to evaluate the effects of a manufacturing change on the identity, strength, quality, purity, and potency of a product as these factors may relate to the safety or effectiveness of the product.

(kk) *Specification*, as used in § 601.12 of this chapter, means the quality standard (i.e., tests, analytical procedures, and acceptance criteria) provided in an approved application to confirm the quality of products, intermediates, raw materials, reagents, components, in-process materials, container closure systems, and other materials used in the production of a product. For the purpose of this definition, *acceptance criteria* means numerical limits, ranges, or other criteria for the tests described.

(ll) *Complete response letter* means a written communication to an applicant from FDA usually describing all of the deficiencies that the agency has identified in a biologics license application

or supplement that must be satisfactorily addressed before it can be approved.

(mm) *Resubmission* means a submission by the biologics license applicant or supplement applicant of all materials needed to fully address all deficiencies identified in the complete response letter. A biologics license application or supplement for which FDA issued a complete response letter, but which was withdrawn before approval and later submitted again, is not a resubmission.

[38 FR 32048, Nov. 20, 1973, as amended at 40 FR 31313, July 25, 1975; 55 FR 11014, Mar. 26, 1990; 61 FR 24232, May 14, 1996; 62 FR 39901, July 24, 1997; 64 FR 56449, Oct. 20, 1999; 65 FR 66634, Nov. 7, 2000; 69 FR 18766, Apr. 8, 2004; 70 FR 14982, Mar. 24, 2005; 73 FR 39610, July 10, 2008; 77 FR 26174, May 3, 2012]

Subpart B—Establishment Standards

§ 600.10 Personnel.

(a) [Reserved]

(b) *Personnel.* Personnel shall have capabilities commensurate with their assigned functions, a thorough understanding of the manufacturing operations which they perform, the necessary training and experience relating to individual products, and adequate information concerning the application of the pertinent provisions of this subchapter to their respective functions. Personnel shall include such professionally trained persons as are necessary to insure the competent performance of all manufacturing processes.

(c) *Restrictions on personnel*—(1) *Specific duties.* Persons whose presence can affect adversely the safety and purity of a product shall be excluded from the room where the manufacture of a product is in progress.

(2) *Sterile operations.* Personnel performing sterile operations shall wear clean or sterilized protective clothing and devices to the extent necessary to protect the product from contamination.

(3) *Pathogenic viruses and spore-forming organisms.* Persons working with viruses pathogenic for man or with spore-forming microorganisms, and persons engaged in the care of animals or animal quarters, shall be excluded from areas where other products are manufactured, or such persons shall change outer clothing, including shoes, or wear protective covering prior to entering such areas.

(4) *Live vaccine work areas.* Persons may not enter a live vaccine processing area after having worked with other infectious agents in any other laboratory during the same working day. Only persons actually concerned with propagation of the culture, production of the vaccine, and unit maintenance, shall be allowed in live vaccine processing areas when active work is in progress. Casual visitors shall be excluded from such units at all times and all others having business in such areas shall be admitted only under supervision. Street clothing, including shoes, shall be replaced or covered by suitable laboratory clothing before entering a live vaccine processing unit. Persons caring for animals used in the manufacture of live vaccines shall be excluded from other animal quarters and from contact with other animals during the same working day.

[38 FR 32048, Nov. 20, 1973, as amended at 49 FR 23833, June 8, 1984; 55 FR 11014, Mar. 26, 1990; 62 FR 53538, Oct. 15, 1997; 68 FR 75119, Dec. 30, 2003]

§ 600.11 Physical establishment, equipment, animals, and care.

(a) *Work areas.* All rooms and work areas where products are manufactured or stored shall be kept orderly, clean, and free of dirt, dust, vermin and objects not required for manufacturing. Precautions shall be taken to avoid clogging and back-siphonage of drainage systems. Precautions shall be taken to exclude extraneous infectious agents from manufacturing areas. Work rooms shall be well lighted and ventilated. The ventilation system shall be arranged so as to prevent the dissemination of microorganisms from one manufacturing area to another and to avoid other conditions unfavorable to the safety of the product. Filling rooms, and other rooms where open, sterile operations are conducted, shall be adequate to meet manufacturing needs and such rooms shall be constructed and equipped to permit thorough cleaning and to keep air-borne

contaminants at a minimum. If such rooms are used for other purposes, they shall be cleaned and prepared prior to use for sterile operations. Refrigerators, incubators and warm rooms shall be maintained at temperatures within applicable ranges and shall be free of extraneous material which might affect the safety of the product.

(b) *Equipment.* Apparatus for sterilizing equipment and the method of operation shall be such as to insure the destruction of contaminating microorganisms. The effectiveness of the sterilization procedure shall be no less than that achieved by an attained temperature of 121.5 °C maintained for 20 minutes by saturated steam or by an attained temperature of 170 °C maintained for 2 hours with dry heat. Processing and storage containers, filters, filling apparatus, and other pieces of apparatus and accessory equipment, including pipes and tubing, shall be designed and constructed to permit thorough cleaning and, where possible, inspection for cleanliness. All surfaces that come in contact with products shall be clean and free of surface solids, leachable contaminants, and other materials that will hasten the deterioration of the product or otherwise render it less suitable for the intended use. For products for which sterility is a factor, equipment shall be sterile, unless sterility of the product is assured by subsequent procedures.

(c) *Laboratory and bleeding rooms.* Rooms used for the processing of products, including bleeding rooms, shall be effectively fly-proofed and kept free of flies and vermin. Such rooms shall be so constructed as to insure freedom from dust, smoke and other deleterious substances and to permit thorough cleaning and disinfection. Rooms for animal injection and bleeding, and rooms for smallpox vaccine animals, shall be disinfected and be provided with the necessary water, electrical and other services.

(d) *Animal quarters and stables.* Animal quarters, stables and food storage areas shall be of appropriate construction, fly-proofed, adequately lighted and ventilated, and maintained in a clean, vermin-free and sanitary condition. No manure or refuse shall be stored as to permit the breeding of flies on the premises, nor shall the establishment be located in close proximity to off-property manure or refuse storage capable of engendering fly breeding.

(e) *Restrictions on building and equipment use*—(1) *Work of a diagnostic nature.* Laboratory procedures of a clinical diagnostic nature involving materials that may be contaminated, shall not be performed in space used for the manufacture of products except that manufacturing space which is used only occasionally may be used for diagnostic work provided spore-forming pathogenic microorganisms are not involved and provided the space is thoroughly cleaned and disinfected before the manufacture of products is resumed.

(2) *Spore-forming organisms for supplemental sterilization procedure control test.* Spore-forming organisms used as an additional control in sterilization procedures may be introduced into areas used for the manufacture of products, only for the purposes of the test and only immediately before use for such purposes: *Provided,* That (i) the organism is not pathogenic for man or animals and does not produce pyrogens or toxins, (ii) the culture is demonstrated to be pure, (iii) transfer of test cultures to culture media shall be limited to the sterility test area or areas designated for work with spore-forming organisms, (iv) each culture be labeled with the name of the microorganism and the statement "Caution: microbial spores. See directions for storage, use and disposition.", and (v) the container of each culture is designed to withstand handling without breaking.

(3) *Work with spore-forming microorganisms.* (i) Manufacturing processes using spore-forming microorganisms conducted in a multiproduct manufacturing site must be performed under appropriate controls to prevent contamination of other products and areas within the site. Prevention of spore contamination can be achieved by using a separate dedicated building or by using process containment if manufacturing is conducted in a multiproduct manufacturing building. All product and personnel movement between the area where the spore-forming microorganisms are manufactured

and other manufacturing areas must be conducted under conditions that will prevent the introduction of spores into other areas of the facility.

(ii) If process containment is employed in a multiproduct manufacturing area, procedures must be in place to demonstrate adequate removal of the spore-forming microorganism(s) from the manufacturing area for subsequent manufacture of other products. These procedures must provide for adequate removal or decontamination of the spore-forming microorganisms on and within manufacturing equipment, facilities, and ancillary room items as well as the removal of disposable or product dedicated items from the manufacturing area. Environmental monitoring specific for the spore-forming microorganism(s) must be conducted in adjacent areas during manufacturing operations and in the manufacturing area after completion of cleaning and decontamination.

(4) *Live vaccine processing.* Live vaccine processing must be performed under appropriate controls to prevent cross contamination of other products and other manufacturing areas within the building. Appropriate controls must include, at a minimum:

(i)(A) Using a dedicated manufacturing area that is either in a separate building, in a separate wing of a building, or in quarters at the blind end of a corridor and includes adequate space and equipment for all processing steps up to, but not including, filling into final containers; and

(B) Not conducting test procedures that potentially involve the presence of microorganisms other than the vaccine strains or the use of tissue culture cell lines other than primary cultures in space used for processing live vaccine; or

(ii) If manufacturing is conducted in a multiproduct manufacturing building or area, using procedural controls, and where necessary, process containment. Process containment is deemed to be necessary unless procedural controls are sufficient to prevent cross contamination of other products and other manufacturing areas within the building. Process containment is a system designed to mechanically isolate equipment or an area that involves manufacturing using live vaccine organisms. All product, equipment, and personnel movement between distinct live vaccine processing areas and between live vaccine processing areas and other manufacturing areas, up to, but not including, filling in final containers, must be conducted under conditions that will prevent cross contamination of other products and manufacturing areas within the building, including the introduction of live vaccine organisms into other areas. In addition, written procedures and effective processes must be in place to adequately remove or decontaminate live vaccine organisms from the manufacturing area and equipment for subsequent manufacture of other products. Written procedures must be in place for verification that processes to remove or decontaminate live vaccine organisms have been followed.

(5) *Equipment and supplies—contamination.* Equipment and supplies used in work on or otherwise exposed to any pathogenic or potentially pathogenic agent shall be kept separated from equipment and supplies used in the manufacture of products to the extent necessary to prevent cross-contamination.

(f) *Animals used in manufacture*—(1) *Care of animals used in manufacturing.* Caretakers and attendants for animals used for the manufacture of products shall be sufficient in number and have adequate experience to insure adequate care. Animal quarters and cages shall be kept in sanitary condition. Animals on production shall be inspected daily to observe response to production procedures. Animals that become ill for reasons not related to production shall be isolated from other animals and shall not be used for production until recovery is complete. Competent veterinary care shall be provided as needed.

(2) *Quarantine of animals*—(i) *General.* No animal shall be used in processing unless kept under competent daily inspection and preliminary quarantine for a period of at least 7 days before use, or as otherwise provided in this subchapter. Only healthy animals free from detectable communicable diseases shall be used. Animals must remain in

overt good health throughout the quarantine periods and particular care shall be taken during the quarantine periods to reject animals of the equine genus which may be infected with glanders and animals which may be infected with tuberculosis.

(ii) *Quarantine of monkeys.* In addition to observing the pertinent general quarantine requirements, monkeys used as a source of tissue in the manufacture of vaccine shall be maintained in quarantine for at least 6 weeks prior to use, except when otherwise provided in this part. Only monkeys that have reacted negatively to tuberculin at the start of the quarantine period and again within 2 weeks prior to use shall be used in the manufacture of vaccine. Due precaution shall be taken to prevent cross-infection from any infected or potentially infected monkeys on the premises. Monkeys to be used in the manufacture of a live vaccine shall be maintained throughout the quarantine period in cages closed on all sides with solid materials except the front which shall be screened, with no more than two monkeys housed in one cage. Cage mates shall not be interchanged.

(3) *Immunization against tetanus.* Horses and other animals susceptible to tetanus, that are used in the processing steps of the manufacture of biological products, shall be treated adequately to maintain immunity to tetanus.

(4) *Immunization and bleeding of animals used as a source of products.* Toxins or other nonviable antigens administered in the immunization of animals used in the manufacture of products shall be sterile. Viable antigens, when so used, shall be free of contaminants, as determined by appropriate tests prior to use. Injections shall not be made into horses within 6 inches of bleeding site. Horses shall not be bled for manufacturing purposes while showing persistent general reaction or local reaction near the site of bleeding. Blood shall not be used if it was drawn within 5 days of injecting the animals with viable microorganisms. Animals shall not be bled for manufacturing purposes when they have an intercurrent disease. Blood intended for use as a source of a biological product shall be collected in clean, sterile vessels. When the product is intended for use by injection, such vessels shall also be pyrogen-free.

(5) [Reserved]

(6) *Reporting of certain diseases.* In cases of actual or suspected infection with foot and mouth disease, glanders, tetanus, anthrax, gas gangrene, equine infectious anemia; equine encephalomyelitis, or any of the pock diseases among animals intended for use or used in the manufacture of products, the manufacturer shall immediately notify the Director, Center for Biologics Evaluation and Research or the Director, Center for Drug Evaluation and Research (see mailing addresses in § 600.2).

(7) *Monkeys used previously for experimental or test purposes.* Monkeys that have been used previously for experimental or test purposes with live microbiological agents shall not be used as a source of kidney tissue for the manufacture of vaccine. Except as provided otherwise in this subchapter, monkeys that have been used previously for other experimental or test purposes may be used as a source of kidney tissue upon their return to a normal condition, provided all quarantine requirements have been met.

(8) *Necropsy examination of monkeys.* Each monkey used in the manufacture of vaccine shall be examined at necropsy under the direction of a qualified pathologist, physician, or veterinarian having experience with diseases of monkeys, for evidence of ill health, particularly for (i) evidence of tuberculosis, (ii) presence of herpes-like lesions, including eruptions or plaques on or around the lips, in the buccal cavity or on the gums, and (iii) signs of conjunctivitis. If there are any such signs or other significant gross pathological lesions, the tissue shall not be used in the manufacture of vaccine.

(g) *Filling procedures.* Filling procedures shall be such as will not affect adversely the safety, purity or potency of the product.

(h) *Containers and closures.* All final containers and closures shall be made of material that will not hasten the deterioration of the product or otherwise render it less suitable for the intended use. All final containers and closures shall be clean and free of surface solids,

leachable contaminants and other materials that will hasten the deterioration of the product or otherwise render it less suitable for the intended use. After filling, sealing shall be performed in a manner that will maintain the integrity of the product during the dating period. In addition, final containers and closures for products intended for use by injection shall be sterile and free from pyrogens. Except as otherwise provided in the regulations of this subchapter, final containers for products intended for use by injection shall be colorless and sufficiently transparent to permit visual examination of the contents under normal light. As soon as possible after filling final containers shall be labeled as prescribed in § 610.60 *et seq.* of this chapter, except that final containers may be stored without such prescribed labeling provided they are stored in a sealed receptacle labeled both inside and outside with at least the name of the product, the lot number, and the filling identification.

[38 FR 32048, Nov. 20, 1973, as amended at 41 FR 10428, Mar. 11, 1976; 49 FR 23833, June 8, 1984; 55 FR 11013, Mar. 26, 1990; 68 FR 75119, Dec. 30, 2003; 70 FR 14982, Mar. 24, 2005; 72 FR 59003, Oct. 18, 2007]

§ 600.12 Records.

(a) *Maintenance of records.* Records shall be made, concurrently with the performance, of each step in the manufacture and distribution of products, in such a manner that at any time successive steps in the manufacture and distribution of any lot may be traced by an inspector. Such records shall be legible and indelible, shall identify the person immediately responsible, shall include dates of the various steps, and be as detailed as necessary for clear understanding of each step by one experienced in the manufacture of products.

(b) *Records retention*—(1) *General.* Records shall be retained for such interval beyond the expiration date as is necessary for the individual product, to permit the return of any clinical report of unfavorable reactions. The retention period shall be no less than five years after the records of manufacture have been completed or six months after the latest expiration date for the individual product, whichever represents a later date.

(2) *Records of recall.* Complete records shall be maintained pertaining to the recall from distribution of any product upon notification by the Director, Center for Biologics Evaluation and Research or the Director, Center for Drug Evaluation and Research, to recall for failure to conform with the standards prescribed in the regulations of this subchapter, because of deterioration of the product or for any other factor by reason of which the distribution of the product would constitute a danger to health.

(3) *Suspension of requirement for retention.* The Director, Center for Biologics Evaluation and Research or the Director, Center for Drug Evaluation and Research, may authorize the suspension of the requirement to retain records of a specific manufacturing step upon a showing that such records no longer have significance for the purposes for which they were made: *Provided,* That a summary of such records shall be retained.

(c) *Records of sterilization of equipment and supplies.* Records relating to the mode of sterilization, date, duration, temperature and other conditions relating to each sterilization of equipment and supplies used in the processing of products shall be made by means of automatic recording devices or by means of a system of recording which gives equivalent assurance of the accuracy and reliability of the record. Such records shall be maintained in a manner that permits an identification of the product with the particular manufacturing process to which the sterilization relates.

(d) *Animal necropsy records.* A necropsy record shall be kept on each animal from which a biological product has been obtained and which dies or is sacrificed while being so used.

(e) *Records in case of divided manufacturing responsibility.* If two or more establishments participate in the manufacture of a product, the records of each such establishment must show plainly the degree of its responsibility. In addition, each participating manufacturer shall furnish to the manufacturer who prepares the product in final form for sale, barter or exchange, a

copy of all records relating to the manufacturing operations performed by such participating manufacturer insofar as they concern the safety, purity and potency of the lots of the product involved, and the manufacturer who prepares the product in final form shall retain a complete record of all the manufacturing operations relating to the product.

[38 FR 32048, Nov. 20, 1973, as amended at 49 FR 23833, June 8, 1984; 55 FR 11013, Mar. 26, 1990; 70 FR 14982, Mar. 24, 2005]

§ 600.13 Retention samples.

Manufacturers shall retain for a period of at least 6 months after the expiration date, unless a different time period is specified in additional standards, a quantity of representative material of each lot of each product, sufficient for examination and testing for safety and potency, except Whole Blood, Cryoprecipitated AHF, Platelets, Red Blood Cells, Plasma, and Source Plasma and Allergenic Products prepared to a physician's prescription. Samples so retained shall be selected at random from either final container material, or from bulk and final containers, provided they include at least one final container as a final package, or package-equivalent of such filling of each lot of the product as intended for distribution. Such sample material shall be stored at temperatures and under conditions which will maintain the identity and integrity of the product. Samples retained as required in this section shall be in addition to samples of specific products required to be submitted to the Center for Biologics Evaluation and Research or the Center for Drug Evaluation and Research (see mailing addresses in § 600.2). Exceptions may be authorized by the Director, Center for Biologics Evaluation and Research or the Director, Center for Drug Evaluation and Research, when the lot yields relatively few final containers and when such lots are prepared by the same method in large number and in close succession.

[41 FR 10428, Mar. 11, 1976, as amended at 49 FR 23833, June 8, 1984; 50 FR 4133, Jan. 29, 1985; 55 FR 11013, Mar. 26, 1990; 70 FR 14982, Mar. 24, 2005]

§ 600.14 Reporting of biological product deviations by licensed manufacturers.

(a) *Who must report under this section?* (1) You, the manufacturer who holds the biological product license and who had control over the product when the deviation occurred, must report under this section. If you arrange for another person to perform a manufacturing, holding, or distribution step, while the product is in your control, that step is performed under your control. You must establish, maintain, and follow a procedure for receiving information from that person on all deviations, complaints, and adverse events concerning the affected product.

(2) Exceptions:

(i) Persons who manufacture only in vitro diagnostic products that are not subject to licensing under section 351 of the Public Health Service Act do not report biological product deviations for those products under this section but must report in accordance with part 803 of this chapter;

(ii) Persons who manufacture blood and blood components, including licensed manufacturers, unlicensed registered blood establishments, and transfusion services, do not report biological product deviations for those products under this section but must report under § 606.171 of this chapter;

(iii) Persons who manufacture Source Plasma or any other blood component and use that Source Plasma or any other blood component in the further manufacture of another licensed biological product must report:

(A) Under § 606.171 of this chapter, if a biological product deviation occurs during the manufacture of that Source Plasma or any other blood component; or

(B) Under this section, if a biological product deviation occurs after the manufacture of that Source Plasma or any other blood component, and during manufacture of the licensed biological product.

(b) *What do I report under this section?* You must report any event, and information relevant to the event, associated with the manufacturing, to include testing, processing, packing, labeling, or storage, or with the holding or distribution, of a licensed biological

product, if that event meets all the following criteria:

(1) Either:

(i) Represents a deviation from current good manufacturing practice, applicable regulations, applicable standards, or established specifications that may affect the safety, purity, or potency of that product; or

(ii) Represents an unexpected or unforeseeable event that may affect the safety, purity, or potency of that product; and

(2) Occurs in your facility or another facility under contract with you; and

(3) Involves a distributed biological product.

(c) *When do I report under this section?* You should report a biological product deviation as soon as possible but you must report at a date not to exceed 45 calendar days from the date you, your agent, or another person who performs a manufacturing, holding, or distribution step under your control, acquire information reasonably suggesting that a reportable event has occurred.

(d) *How do I report under this section* You must report on Form FDA–3486.

(e) *Where do I report under this section?* (1) For biological products regulated by the Center for Biologics Evaluation and Research (CBER), send the completed Form FDA–3486 to the Director, Office of Compliance and Biologics Quality (HFM–600) (see mailing addresses in § 600.2), or an electronic filing through CBER's Web site at *http://www.fda.gov/cber/biodev/biodev.htm*.

(2) For biological products regulated by the Center for Drug Evaluation and Research (CDER), send the completed Form FDA–3486 to the Division of Compliance Risk Management and Surveillance (HFD–330) (see mailing addresses in § 600.2). CDER does not currently accept electronic filings.

(3) If you make a paper filing, you should identify on the envelope that a biological product deviation report (BPDR) is enclosed.

(f) *How does this regulation affect other FDA regulations?* This part supplements and does not supersede other provisions of the regulations in this chapter. All biological product deviations, whether or not they are required to be reported under this section, should be investigated in accordance with the applicable provisions of parts 211 and 820 of this chapter.

[65 FR 66634, Nov. 7, 2000, as amended at 70 FR 14982, Mar. 24, 2005]

§ 600.15 Temperatures during shipment.

The following products shall be maintained during shipment at the specified temperatures:

(a) *Products.*

Product	Temperature
Cryoprecipitated AHF	−18 °C or colder.
Measles and Rubella Virus Vaccine Live	10 °C or colder.
Measles Live and Smallpox Vaccine	Do.
Measles, Mumps, and Rubella Virus Vaccine Live	Do.
Measles and Mumps Virus Vaccine Live	Do.
Measles Virus Vaccine Live	Do.
Mumps Virus Vaccine Live	Do.
Fresh Frozen Plasma	−18 °C or colder.
Liquid Plasma	1 to 10 °C.
Plasma	−18 °C or colder.
Platelet Rich Plasma	Between 1 and 10 °C if the label indicates storage between 1 and 6 °C, or all reasonable methods to maintain the temperature as close as possible to a range between 20 and 24 °C, if the label indicates storage between 20 and 24 °C.
Platelets	Between 1 and 10 °C if the label indicates storage between 1 and 6 °C, or all reasonable methods to maintain the temperature as close as possible to a range between 20 to 24 °C, if the label indicates storage between 20 and 24 °C.
Poliovirus Vaccine Live Oral Trivalent	0 °C or colder.
Poliovirus Vaccine Live Oral Type I	Do.
Poliovirus Vaccine Live Oral Type II	Do.
Poliovirus Vaccine Live Oral Type III	Do.
Red Blood Cells (liquid product)	Between 1 and 10 °C.
Red Blood Cells Frozen	−65 °C or colder.
Rubella and Mumps Virus Vaccine Live	10 °C or colder.
Rubella Virus Vaccine Live	Do.
Smallpox Vaccine (Liquid Product)	0 °C or colder.
Source Plasma	−5 °C or colder.

Product	Temperature
Source Plasma Liquid	10 °C or colder.
Whole Blood	Blood that is transported from the collecting facility to the processing facility shall be transported in an environment capable of continuously cooling the blood toward a temperature range of 1 to 10 °C, or at a temperature as close as possible to 20 to 24 °C for a period not to exceed 6 hours. Blood transported from the storage facility shall be placed in an appropriate environment to maintain a temperature range between 1 to 10 °C during shipment.
Yellow Fever Vaccine	0 °C or colder.

(b) *Exemptions.* Exemptions or modifications shall be made only upon written approval, in the form of a supplement to the biologics license application, approved by the Director, Center for Biologics Evaluation and Research.

[39 FR 39872, Nov. 12, 1974, as amended at 49 FR 23833, June 8, 1984; 50 FR 4133, Jan. 29, 1985; 50 FR 9000, Mar. 6, 1985; 55 FR 11013, Mar. 26, 1990; 59 FR 49351, Sept. 28, 1994; 64 FR 56449, Oct. 20, 1999]

Subpart C—Establishment Inspection

§ 600.20 Inspectors.

Inspections shall be made by an officer of the Food and Drug Administration having special knowledge of the methods used in the manufacture and control of products and designated for such purposes by the Commissioner of Food and Drugs, or by any officer, agent, or employee of the Department of Health and Human Services specifically designated for such purpose by the Secretary.

[38 FR 32048, Nov. 20, 1973]

§ 600.21 Time of inspection.

The inspection of an establishment for which a biologics license application is pending need not be made until the establishment is in operation and is manufacturing the complete product for which a biologics license is desired. In case the license is denied following inspection for the original license, no reinspection need be made until assurance has been received that the faulty conditions which were the basis of the denial have been corrected. An inspection of each licensed establishment and its additional location(s) shall be made at least once every 2 years. Inspections may be made with or without notice, and shall be made during regular business hours unless otherwise directed.

[38 FR 32048, Nov. 20, 1973, as amended at 48 FR 26314, June 7, 1983; 64 FR 56449, Oct. 20, 1999]

§ 600.22 Duties of inspector.

The inspector shall:

(a) Call upon the active head of the establishment, stating the object of his visit,

(b) Interrogate the proprietor or other personnel of the establishment as he may deem necessary,

(c) Examine the details of location, construction, equipment and maintenance, including stables, barns, warehouses, manufacturing laboratories, bleeding clinics maintained for the collection of human blood, shipping rooms, record rooms, and any other structure or appliance used in any part of the manufacture of a product,

(d) Investigate as fully as he deems necessary the methods of propagation, processing, testing, storing, dispensing, recording, or other details of manufacture and distribution of each licensed product, or product for which a license has been requested, including observation of these procedures in actual operation,

(e) Obtain and cause to be sent to the Director, Center for Biologics Evaluation and Research or the Director, Center for Drug Evaluation and Research (see mailing addresses in § 600.2), adequate samples for the examination of any product or ingredient used in its manufacture,

(f) Bring to the attention of the manufacturer any fault observed in the course of inspection in location, construction, manufacturing methods, or administration of a licensed establishment which might lead to impairment of a product,

(g) Inspect and copy, as circumstances may require, any records required to be kept pursuant to § 600.12.

(h) Certify as to the condition of the establishment and of the manufacturing methods followed and make recommendations as to action deemed appropriate with respect to any application for license or any license previously issued.

[38 FR 32048, Nov. 20, 1973, as amended at 49 FR 23833, June 8, 1984; 55 FR 11013, Mar. 26, 1990; 70 FR 14982, Mar. 24, 2005]

Subpart D—Reporting of Adverse Experiences

SOURCE: 59 FR 54042, Oct. 27, 1994, unless otherwise noted.

§ 600.80 Postmarketing reporting of adverse experiences.

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

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

Blood Component. As defined in § 606.3(c) of this chapter.

Disability. A substantial disruption of a person's ability to conduct normal life functions.

Life-threatening adverse experience. Any adverse experience that places the patient, in the view of the initial reporter, at immediate risk of death from the adverse experience as it occurred, i.e., it does not include an adverse experience that, had it occurred in a more severe form, might have caused death.

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

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

(b) *Review of adverse experiences.* Any person having a biologics license under § 601.20 of this chapter shall promptly review all adverse experience information pertaining to its product obtained or otherwise received by the licensed manufacturer from any source, foreign or domestic, including information derived from commercial marketing experience, postmarketing clinical investigations, postmarketing epidemiological/surveillance studies, reports in the scientific literature, and unpublished scientific papers. Licensed manufacturers are not required to resubmit to

FDA adverse product experience reports forwarded to the licensed manufacturer by FDA; licensed manufacturers, however, must submit all followup information on such reports to FDA. Any person subject to the reporting requirements under paragraph (c) of this section shall also develop written procedures for the surveillance, receipt, evaluation, and reporting of postmarketing adverse experiences to FDA.

(c) *Reporting requirements.* The licensed manufacturer shall report to FDA adverse experience information, as described in this section. The licensed manufacturer shall submit two copies of each report described in this section for nonvaccine biological products to the Center for Biologics Evaluation and Research (HFM–210), or to the Center for Drug Evaluation and Research (see mailing addresses in § 600.2). Submit all vaccine adverse experience reports to: Vaccine Adverse Event Reporting System (VAERS) (see mailing addresses in § 600.2). FDA may waive the requirement for the second copy in appropriate instances.

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

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

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

(A) A copy of all adverse biological product experience reports submitted to the licensed manufacturer of the final product;

(B) The date the report was received by the person;

(C) The date the report was submitted to the licensed manufacturer of the final product; and—

(D) The name and address of the licensed manufacturer of the final product.

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

(2) *Periodic adverse experience reports.* (i) The licensed manufacturer shall report each adverse experience not reported under paragraph (c)(1)(i) of this section at quarterly intervals, for 3 years from the date of issuance of the biologics license, and then at annual intervals. The licensed manufacturer shall submit each quarterly report within 30 days of the close of the quarter (the first quarter beginning on the date of issuance of the biologics license) and each annual report within 60 days of the anniversary date of the issuance of the biologics license. Upon

written notice, FDA may extend or reestablish the requirement that a licensed manufacturer submit quarterly reports, or require that the licensed manufacturer submit reports under this section at different times than those stated. Followup information to adverse experiences submitted in a periodic report may be submitted in the next periodic report.

(ii) Each periodic report shall contain:

(A) A narrative summary and analysis of the information in the report and an analysis of the 15-day Alert reports submitted during the reporting interval (all 15-day Alert reports being appropriately referenced by the licensed manufacturer's patient identification number, adverse reaction term(s), and date of submission to FDA);

(B) A form designated for Adverse Experience Reporting by FDA for each adverse experience not reported under paragraph (c)(1)(i) of this section (with an index consisting of a line listing of the licensed manufacturer's patient identification number and adverse reaction term(s)); and

(C) A history of actions taken since the last report because of adverse experiences (for example, labeling changes or studies initiated).

(iii) Periodic reporting, except for information regarding 15-day Alert reports, does not apply to adverse experience information obtained from postmarketing studies (whether or not conducted under an investigational new drug application), from reports in the scientific literature, and from foreign marketing experience.

(d) *Scientific literature.* (1) A 15-day Alert report based on information from the scientific literature shall be accompanied by a copy of the published article. The 15-day Alert reporting requirements in paragraph (c)(1)(i) of this section (i.e., serious, unexpected adverse experiences) apply only to reports found in scientific and medical journals either as case reports or as the result of a formal clinical trial.

(2) As with all reports submitted under paragraph (c)(1)(i) of this section, reports based on the scientific literature shall be submitted on the reporting form designated by FDA or comparable format as prescribed by paragraph (f) of this section. In cases where the licensed manufacturer believes that preparing the form designated by FDA constitutes an undue hardship, the licensed manufacturer may arrange with the Division of Biostatistics and Epidemiology (HFM–210) for an acceptable alternative reporting format.

(e) *Postmarketing studies.* (1) Licensed manufacturers are not required to submit a 15-day Alert report under paragraph (c) of this section for an adverse experience obtained from a postmarketing clinical study (whether or not conducted under a biological investigational new drug application) unless the licensed manufacturer concludes that there is a reasonable possibility that the product caused the adverse experience.

(2) The licensed manufacturer shall separate and clearly mark reports of adverse experiences that occur during a postmarketing study as being distinct from those experiences that are being reported spontaneously to the licensed manufacturer.

(f) *Reporting forms.* (1) Except as provided in paragraph (f)(3) of this section, the licensed manufacturer shall complete the reporting form designated by FDA for each report of an adverse experience (FDA Form 3500A, or, for vaccines, a VAERS form; foreign events including those associated with the use of vaccines, may be submitted either on an FDA Form 3500A or, if preferred, on a CIOMS I form).

(2) Each completed form should refer only to an individual patient or single attached publication.

(3) Instead of using a designated reporting form, a licensed manufacturer may use a computer-generated form or other alternative format (e.g., a computer-generated tape or tabular listing) provided that:

(i) The content of the alternative format is equivalent in all elements of information to those specified in the form designated by FDA; and

(ii) the format is approved in advance by MEDWATCH: The FDA Medical Products Reporting Program; or, for alternatives to the VAERS Form, by the Division of Biostatistics and Epidemiology.

(4) Copies of the reporting form designated by FDA (FDA–3500A) for nonvaccine biological products may be obtained from *http://www.fda.gov/medwatch/getforms.htm*. Additional supplies of the form may be obtained from the Consolidated Forms and Publications Distribution Center, 3222 Hubbard Rd., Landover, MD 20785. Supplies of the VAERS form may be obtained from VAERS by calling 1–800–822–7967.

(g) *Multiple reports.* A licensed manufacturer should not include in reports under this section any adverse experience that occurred in clinical trials if they were previously submitted as part of the biologics license application. If a report refers to more than one biological product marketed by a licensed manufacturer, the licensed manufacturer should submit the report to the biologics license application for the product listed first in the report.

(h) *Patient privacy.* For nonvaccine biological products, a licensed manufacturer should not include in reports under this section the names and addresses of individual patients; instead, the licensed manufacturer should assign a unique code number to each report, preferably not more than eight characters in length. The licensed manufacturer should include the name of the reporter from whom the information was received. The names of patients, health care professionals, hospitals, and geographical identifiers in adverse experience reports are not releasable to the public under FDA's public information regulations in part 20 this of chapter. For vaccine adverse experience reports, these data will become part of the CDC Privacy Act System 09–20–0136, "Epidemiologic Studies and Surveillance of Disease Problems." Information identifying the person who received the vaccine or that person's legal representative will not be made available to the public, but may be available to the vaccinee or legal representative.

(i) *Recordkeeping.* The licensed manufacturer shall maintain for a period of 10 years records of all adverse experiences known to the licensed manufacturer, including raw data and any correspondence relating to the adverse experiences.

(j) *Revocation of biologics license.* If a licensed manufacturer fails to establish and maintain records and make reports required under this section with respect to a licensed biological product, FDA may revoke the biologics license for such a product in accordance with the procedures of §601.5 of this chapter.

(k) *Exemptions.* Manufacturers of the following listed products are not required to submit adverse experience reports under this section:

(1) Whole blood or components of whole blood.

(2) In vitro diagnostic products, including assay systems for the detection of antibodies or antigens to retroviruses. These products are subject to the reporting requirements for devices.

(l) *Disclaimer.* A report or information submitted by a licensed manufacturer under this section (and any release by FDA of that report or information) does not necessarily reflect a conclusion by the licensed manufacturer or FDA that the report or information constitutes an admission that the biological product caused or contributed to an adverse effect. A licensed manufacturer need not admit, and may deny, that the report or information submitted under this section constitutes an admission that the biological product caused or contributed to an adverse effect. For purposes of this provision, this paragraph also includes any person reporting under paragraph (c)(1)(iii) of this section.

[59 FR 54042, Oct. 27, 1994, as amended at 62 FR 34168, June 25, 1997; 62 FR 52252, Oct. 7, 1997; 63 FR 14612, Mar. 26, 1998; 64 FR 56449, Oct. 20, 1999; 70 FR 14982, Mar. 24, 2005]

EFFECTIVE DATE NOTE: At 79 FR 33090, June 10, 2014, §600.80 was amended as follows, effective June 10, 2015.

a. By removing the word "shall" each time it appears and by adding in its place the word "must";

b. By removing the phrase "licensed manufacturer" or "licensed manufacturers" each time it appears and by adding in its place the word "applicant" or "applicants" respectively;

c. By removing the phrase "Licensed manufacturer" or "Licensed manufacturers" each time it appears and by adding in its place the word "Applicant" or "Applicants" respectively;

d. In paragraph (a) by alphabetically adding the definitions for "Individual case safety report (ICSR)" and "ICSR attachments";

e. In paragraph (c)(1)(i) by removing the phrase "in no case later than 15 calendar days of" and by adding in its place the phrase "no later than 15 calendar days from";

f. In paragraph (c)(1)(ii) by removing the last sentence;

g. By removing paragraph (c)(1)(iv);

h. By revising paragraph (c) introductory text, the first and third sentences of paragraph (c)(1)(iii) introductory text, and paragraph (c)(2)(ii);

i. By removing paragraph (d)(2) and by redesignating paragraph (d)(1) as paragraph (d) and revising the first sentence of paragraph (d);

j. By removing paragraph (e)(2) and by redesignating paragraph (e)(1) as paragraph (e);

k. By revising paragraph (f);

l. By redesignating paragraph (g) through paragraph (*l*) as paragraph (i) through paragraph (n) and by revising newly redesignated paragraph (j); and

m. By adding new paragraphs (g) and (h). For the convenience of the user, the added and revised text is set forth as follows:

§ 600.80 Postmarketing reporting of adverse experiences.

(a) * * *

Individual case safety report (ICSR). A description of an adverse experience related to an individual patient or subject.

ICSR attachments. Documents related to the adverse experience described in an ICSR, such as medical records, hospital discharge summaries, or other documentation.

* * * * *

(c) *Reporting requirements.* The applicant must submit to FDA postmarketing 15-day Alert reports and periodic safety reports pertaining to its biological product as described in this section. These reports must be submitted to the Agency in electronic format as described in paragraph (h)(1) of this section, except as provided in paragraph (h)(2) of this section.

(1) * * *

(iii) *Submission of reports.* The requirements of paragraphs (c)(1)(i) and (c)(1)(ii) of this section, concerning the submission of postmarketing 15-day Alert reports, also apply to any person whose name appears on the label of a licensed biological product as a manufacturer, packer, distributor, shared manufacturer, joint manufacturer, or any other participant involved in divided manufacturing. * * * If a person elects to submit adverse experience reports to the applicant rather than to FDA, the person must submit, by any appropriate means, each report to the applicant within 5 calendar days of initial receipt of the information by the person, and the applicant must then comply with the requirements of this section. * * *

* * * * *

(2) * * *

(ii) Each periodic report is required to contain:

(A) *Descriptive information.* (*1*) A narrative summary and analysis of the information in the report;

(*2*) An analysis of the 15-day Alert reports submitted during the reporting interval (all 15-day Alert reports being appropriately referenced by the applicant's patient identification code for nonvaccine biological product reports or by the unique case identification number for vaccine reports, adverse reaction term(s), and date of submission to FDA);

(*3*) A history of actions taken since the last report because of adverse experiences (for example, labeling changes or studies initiated);

(*4*) An index consisting of a line listing of the applicant's patient identification code for nonvaccine biological product reports or by the unique case identification number for vaccine reports and adverse reaction term(s) for ICSRs submitted under paragraph (c)(2)(ii)(B) of this section; and

(B) *ICSRs for serious, expected and, nonserious adverse experiences.* An ICSR for each adverse experience not reported under paragraph (c)(1)(i) of this section (all serious, expected and nonserious adverse experiences). All such ICSRs must be submitted to FDA (either individually or in one or more batches) within the timeframe specified in paragraph (c)(2)(i) of this section. ICSRs must only be submitted to FDA once.

* * * * *

(d) *Scientific literature.* A 15-day Alert report based on information in the scientific literature must be accompanied by a copy of the published article. * * *

* * * * *

(f) *Information reported on ICSRs for nonvaccine biological products.* ICSRs for nonvaccine biological products include the following information:

(1) *Patient information.*

(i) Patient identification code;

(ii) Patient age at the time of adverse experience, or date of birth;

(iii) Patient gender; and

(iv) Patient weight.

(2) *Adverse experience.*

(i) Outcome attributed to adverse experience;

(ii) Date of adverse experience;

(iii) Date of report;

(iv) Description of adverse experience (including a concise medical narrative);

(v) Adverse experience term(s);
(vi) Description of relevant tests, including dates and laboratory data; and
(vii) Other relevant patient history, including preexisting medical conditions.
(3) *Suspect medical product(s).*
(i) Name;
(ii) Dose, frequency, and route of administration used;
(iii) Therapy dates;
(iv) Diagnosis for use (indication);
(v) Whether the product is a combination product as defined in §3.2(e) of this chapter;
(vi) Whether the product is a prescription or nonprescription product;
(vii) Whether adverse experience abated after product use stopped or dose reduced;
(viii) Whether adverse experience reappeared after reintroduction of the product;
(ix) Lot number;
(x) Expiration date;
(xi) National Drug Code (NDC) number, or other unique identifier; and
(xii) Concomitant medical products and therapy dates.
(4) *Initial reporter information.*
(i) Name, address, and telephone number;
(ii) Whether the initial reporter is a health care professional; and
(iii) Occupation, if a health care professional.
(5) *Applicant information.*
(i) Applicant name and contact office address;
(ii) Telephone number;
(iii) Report source, such as spontaneous, literature, or study;
(iv) Date the report was received by applicant;
(v) Application number and type;
(vi) Whether the ICSR is a 15-day "Alert report";
(vii) Whether the ICSR is an initial report or followup report; and
(viii) Unique case identification number, which must be the same in the initial report and any subsequent followup report(s).
(g) *Information reported on ICSRs for vaccine products.* ICSRs for vaccine products include the following information:
(1) *Patient information.*
(i) Patient name, address, telephone number;
(ii) Patient age at the time of vaccination, or date of birth;
(iii) Patient gender; and
(iv) Patient birth weight for children under age 5.
(2) *Adverse experience.*
(i) Outcome attributed to adverse experience;
(ii) Date and time of adverse experience;
(iii) Date of report;
(iv) Description of adverse experience (including a concise medical narrative);
(v) Adverse experience term(s);
(vi) Illness at the time of vaccination;
(vii) Description of relevant tests, including dates and laboratory data; and
(viii) Other relevant patient history, including preexisting medical conditions.
(3) *Suspect medical product(s), including vaccines administered on the same date.*
(i) Name;
(ii) Dose, frequency, and route or site of administration used;
(iii) Number of previous vaccine doses;
(iv) Vaccination date(s) and time(s);
(v) Diagnosis for use (indication);
(vi) Whether the product is a combination product (as defined in §3.2(e) of this chapter);
(vii) Whether the adverse experience abated after product use stopped or dose reduced;
(viii) Whether the adverse experience reappeared after reintroduction of the product;
(ix) Lot number;
(x) Expiration date;
(xi) National Drug Code (NDC) number, or other unique identifier; and
(xii) Concomitant medical products and therapy dates.
(4) *Vaccine(s) administered in the 4 weeks prior to the vaccination date.*
(i) Name of vaccine;
(ii) Manufacturer;
(iii) Lot number;
(iv) Route or site of administration;
(v) Date given; and
(vi) Number of previous doses.
(5) *Initial reporter information.*
(i) Name, address, and telephone number;
(ii) Whether the initial reporter is a health care professional; and
(iii) Occupation, if a health care professional.
(6) *Facility and personnel where vaccine was administered.*
(i) Name of person who administered vaccine;
(ii) Name of responsible physician at facility where vaccine was administered; and
(iii) Name, address (including city, county, and state), and telephone number of facility where vaccine was administered.
(7) *Applicant information.*
(i) Applicant name and contact office address;
(ii) Telephone number;
(iii) Report source, such as spontaneous, literature, or study;
(iv) Date received by applicant;
(v) Application number and type;
(vi) Whether the ICSR is a 15-day "Alert report";
(vii) Whether the ICSR is an initial report or followup report; and
(viii) Unique case identification number, which must be the same in the initial report and any subsequent followup report(s).
(h) *Electronic format for submissions.* (1) Safety report submissions, including ICSRs, ICSR attachments, and the descriptive information in periodic reports, must be in an

electronic format that FDA can process, review, and archive. FDA will issue guidance on how to provide the electronic submission (e.g., method of transmission, media, file formats, preparation and organization of files).

(2) Persons subject to the requirements of paragraph (c) of this section may request, in writing, a temporary waiver of the requirements in paragraph (h)(1) of this section. These waivers will be granted on a limited basis for good cause shown. FDA will issue guidance on requesting a waiver of the requirements in paragraph (h)(1) of this section. Requests for waivers must be submitted in accordance with § 600.90.

* * * * *

(j) *Patient privacy.* For nonvaccine biological products, an applicant should not include in reports under this section the names and addresses of individual patients; instead, the applicant should assign a unique code for identification of the patient. The applicant should include the name of the reporter from whom the information was received as part of the initial reporter information, even when the reporter is the patient. The names of patients, health care professionals, hospitals, and geographical identifiers in adverse experience reports are not releasable to the public under FDA's public information regulations in part 20 of this chapter. For vaccine adverse experience reports, these data will become part of the CDC Privacy Act System 09–20–0136, "Epidemiologic Studies and Surveillance of Disease Problems." Information identifying the person who received the vaccine or that person's legal representative will not be made available to the public, but may be available to the vaccinee or legal representative.

* * * * *

§ 600.81 Distribution reports.

The licensed manufacturer shall submit to the Center for Biologics Evaluation and Research or the Center for Drug Evaluation and Research (see mailing addresses in § 600.2), information about the quantity of the product distributed under the biologics license, including the quantity distributed to distributors. The interval between distribution reports shall be 6 months. Upon written notice, FDA may require that the licensed manufacturer submit distribution reports under this section at times other than every 6 months. The distribution report shall consist of the bulk lot number (from which the final container was filled), the fill lot numbers for the total number of dosage units of each strength or potency distributed (e.g., fifty thousand per 10-milliliter vials), the label lot number (if different from fill lot number), labeled date of expiration, number of doses in fill lot/label lot, date of release of fill lot/label lot for distribution at that time. If any significant amount of a fill lot/label lot is returned, include this information. Disclosure of financial or pricing data is not required. As needed, FDA may require submission of more detailed product distribution information. Upon written notice, FDA may require that the licensed manufacturer submit reports under this section at times other than those stated. Requests by a licensed manufacturer to submit reports at times other than those stated should be made as a request for a waiver under § 600.90.

[59 FR 54042, Oct. 27, 1994, as amended at 64 FR 56449, Oct. 20, 1999; 70 FR 14983, Mar. 24, 2005]

EFFECTIVE DATE NOTE: At 79 FR 33091, June 10, 2014, § 600.81 was amended as follows, effective June 10, 2015.

a. By removing the phrase "licensed manufacturer" each time it appears and by adding in its place the word "applicant";

b. By removing the word "shall" each time it appears and by adding in its place the word "must";

c. By designating the existing text as paragraph (a) and by adding a heading for newly designated paragraph (a);

d. In newly designated paragraph (a), by removing from the first sentence the phrase "(see mailing addresses in § 600.2)"; and

e. By adding new paragraph (b). For the convenience of the user, the added and revised text is set forth as follows:

§ 600.81 Distribution reports.

(a) *Reporting requirements.* * * *

(b)(1) *Electronic format.* Except as provided for in paragraph (b)(2) of this section, the distribution reports required under paragraph (a) of this section must be submitted to the Agency in an electronic format that FDA can process, review, and archive. FDA will issue guidance on how to provide the electronic submission (e.g., method of transmission, media, file formats, preparation and organization of files).

(2) *Waivers.* An applicant may request, in writing, a temporary waiver of the requirements in paragraph (b)(1) of this section. These waivers will be granted on a limited basis for good cause shown. FDA will issue

guidance on requesting a waiver of the requirements in paragraph (b)(1) of this section. Requests for waivers must be submitted in accordance with § 600.90.

§ 600.90 Waivers.

(a) A licensed manufacturer may ask the Food and Drug Administration to waive under this section any requirement that applies to the licensed manufacturer under §§ 600.80 and 600.81. A waiver request under this section is required to be submitted with supporting documentation. The waiver request is required to contain one of the following:

(1) An explanation why the licensed manufacturer's compliance with the requirement is unnecessary or cannot be achieved,

(2) A description of an alternative submission that satisfies the purpose of the requirement, or

(3) Other information justifying a waiver.

(b) FDA may grant a waiver if it finds one of the following:

(1) The licensed manufacturer's compliance with the requirement is unnecessary or cannot be achieved,

(2) The licensed manufacturer's alternative submission satisfies the requirement, or

(3) The licensed manufacturer's submission otherwise justifies a waiver.

EFFECTIVE DATE NOTE: At 79 FR 33092, June 10, 2014, § 600.90 was amended by removing the phrase "licensed manufacturer" or "licensed manufacturer's" each time it appears and by adding in its place the word "applicant" or "applicant's" respectively, effective June 10, 2015.

PART 601—LICENSING

Subpart A—General Provisions

Subpart B [Reserved]

Subpart C—Biologics Licensing

Subpart D—Diagnostic Radiopharmaceuticals

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

Subpart F—Confidentiality of Information

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.

CROSS REFERENCES: For U.S. Customs Service regulations relating to viruses, serums, and toxins, see 19 CFR 12.21–12.23. For U.S. Postal Service regulations relating to the admissibility to the United States mails see parts 124 and 125 of the Domestic Mail Manual, that is incorporated by reference in 39 CFR part 111.

Subpart A—General Provisions

§ 601.2 Applications for biologics licenses; procedures for filing.

(a) *General.* To obtain a biologics license under section 351 of the Public Health Service Act for any biological product, the manufacturer shall submit an application to the Director, Center for Biologics Evaluation and Research 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. 201 *et seq.*) that has not been revoked or suspended as of December 20, 1999, shall constitute an approved biologics license application in effect under the same terms and conditions set forth in such product license and such portions of the establishment license relating to such product.

[64 FR 56450, Oct. 20, 1999, as amended at 70 FR 14983, Mar. 24, 2005]

§ 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]

§ 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]

§ 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]

§ 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]

§ 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]

§ 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]

§ 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

§ 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 Effected in 30 Days" or, if applicable under paragraph (c)(5) of this section, "Supplement—Changes Being Effected."

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

(i) [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 Effected" supplement or a situation in which the applicant presents evidence that the proposed change has been validated in accordance with an approved protocol for such change under paragraph (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]

§ 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]

§ 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]

§ 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]

§ 601.21 Products under development.

A biological product undergoing development, but not yet ready for a biologics license, may be shipped or otherwise delivered from one State or possession into another State or possession provided such shipment or delivery is not for introduction or delivery

for introduction into interstate commerce, except as provided in sections 505(i) and 520(g) of the Federal Food, Drug, and Cosmetic Act, as amended, and the regulations thereunder (21 CFR parts 312 and 812).

[64 FR 56451, Oct. 20, 1999]

§ 601.22 Products in short supply; initial manufacturing at other than licensed location.

A biologics license issued to a manufacturer and covering all locations of manufacture shall authorize persons other than such manufacturer to conduct at places other than such locations the initial, and partial manufacturing of a product for shipment solely to such manufacturer only to the extent that the names of such persons and places are registered with the Commissioner of Food and Drugs and it is found upon application of such manufacturer, that the product is in short supply due either to the peculiar growth requirements of the organism involved or to the scarcity of the animal required for manufacturing purposes, and such manufacturer has established with respect to such persons and places such procedures, inspections, tests or other arrangements as will ensure full compliance with the applicable regulations of this subchapter related to continued safety, purity, and potency. Such persons and places shall be subject to all regulations of this subchapter except §§ 601.2 to 601.6, 601.9, 601.10, 601.20, 601.21 to 601.33, and 610.60 to 610.65 of this chapter. For persons and places authorized under this section to conduct the initial and partial manufacturing of a product for shipment solely to a manufacturer of a product subject to licensure under § 601.2(c), the following additional regulations shall not be applicable: §§ 600.10(b) and (c), 600.11, 600.12, 600.13, 610.11, and 610.53 of this chapter. Failure of such manufacturer to maintain such procedures, inspections, tests, or other arrangements, or failure of any person conducting such partial manufacturing to comply with applicable regulations shall constitute a ground for suspension or revocation of the authority conferred pursuant to this section on the same basis as provided in §§ 601.6 to 601.8 with respect to the suspension and the revocation of licenses.

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

§ 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 8½ × 11 inches. The time allotted for submissions will be 60 days, unless otherwise indicated in the specific notice requesting data and views for a particular category of biological products. When requested, abbreviated submissions should be sent. All submissions shall be in the following format, indicating "none" or "not applicable" where appropriate, unless changed in the FEDERAL REGISTER notice:

BIOLOGICAL PRODUCTS REVIEW INFORMATION

I. Label or labels and all other labeling (preferably mounted. Facsimile labeling is acceptable in lieu of actual container labeling), including labeling for export.

II. Representative advertising used during the past 5 years.

III. The complete quantitative composition of the biological product.

IV. Animal safety data.

A. Individual active components.

1. Controlled studies.

2. Partially controlled or uncontrolled studies.

B. Combinations of the individual active components.

1. Controlled studies.

2. Partially controlled or uncontrolled studies.

C. Finished biological product.

1. Controlled studies.

2. Partially controlled or uncontrolled studies.

V. Human safety data.

A. Individual active components.

1. Controlled studies.

2. Partially controlled or uncontrolled studies.

3. Documented case reports.

4. Pertinent marketing experiences that may influence a determination as to the safety of each individual active component.

5. Pertinent medical and scientific literature.

B. Combinations of the individual active components.

1. Controlled studies.

2. Partially controlled or uncontrolled studies.

3. Documented case reports.

4. Pertinent marketing experiences that may influence a determination as to the safety of combinations of the individual active components.

5. Pertinent medical and scientific literature.

C. Finished biological product.

1. Controlled studies.

2. Partially controlled or uncontrolled studies.

3. Documented case reports.

4. Pertinent marketing experiences that may influence a determination as to the safety of the finished biological product.

5. Pertinent medical and scientific literature.

VI. Efficacy data.

A. Individual active components.

1. Controlled studies.

2. Partially controlled or uncontrolled studies.

3. Documented case reports.

4. Pertinent marketing experiences that may influence a determination on the efficacy of each individual active component.

5. Pertinent medical and scientific literature.

B. Combinations of the individual active components.

1. Controlled studies.

2. Partially controlled or uncontrolled studies.

3. Documented case reports.

4. Pertinent marketing experiences that may influence a determination as to the effectiveness of combinations of the individual active components.

5. Pertinent medical and scientific literature.

C. Finished biological product.

1. Controlled studies.

2. Partially controlled or uncontrolled studies.

3. Documented case reports.

4. Pertinent marketing experiences that may influence a determination as to the effectiveness of the finished biological product.

5. Pertinent medical and scientific literature.

VII. A summary of the data and views setting forth the medical rational and purpose (or lack thereof) for the biological product and its components and the scientific basis (or lack thereof) for the conclusion that the biological product, including its components, has been proven safe and effective and is properly labeled for the intended use or uses. If there is an absence of controlled studies in the materials submitted, an explanation as to why such studies are not considered necessary or feasible shall be included.

VIII. If the submission is by a licensed manufacturer, a statement signed by the authorized official of the licensed manufacturer shall be included, stating that to the best of his or her knowledge and belief, it includes all information, favorable and unfavorable, pertinent to an evaluation of the safety, effectiveness, and labeling of the product, including information derived from investigation, commercial marketing, or published literature. If the submission is by an interested person other than a licensed manufacturer, a statement signed by the person responsible for such submission shall be included, stating that to the best of his knowledge and belief, it fairly reflects a balance of all the available information, favorable and unfavorable available to him, pertinent to an evaluation of the safety, effectiveness, and labeling of the product.

(c) *Deliberations of an advisory review panel.* An advisory review panel will meet as often and for as long as is appropriate to review the data submitted to it and to prepare a report containing its conclusions and recommendations to the Commissioner of Food and Drugs with respect to the safety, effectiveness, and labeling of the biological products in the designated category under review.

(1) A panel may also consult any individual or group.

(2) Any interested person may request in writing an opportunity to present oral views to the panel. Such written requests for oral presentations should include a summarization of the data to be presented to the panel. Such request may be granted or denied by the panel.

(3) Any interested person may present written data and views which shall be considered by the panel. This information shall be presented to the panel in the format set forth in paragraph (b)(3) of this section and within the time period established for the biological product category in the notice for review by a panel.

(d) *Standards for safety, effectiveness, and labeling.* The advisory review panel, in reviewing the submitted data and preparing the panel's conclusions and recommendations, and the Commissioner of Food and Drugs, in reviewing and implementing the conclusions and recommendations of the panel, shall apply the following standards to determine that a biological product is safe and effective and not misbranded.

(1) Safety means the relative freedom from harmful effect to persons affected, directly or indirectly, by a product when prudently administered, taking into consideration the character of the product in relation to the condition of the recipient at the time. Proof of safety shall consist of adequate tests by methods reasonably applicable to show the biological product is safe under the prescribed conditions of use, including results of significant human experience during use.

(2) Effectiveness means a reasonable expectation that, in a significant proportion of the target population, the pharmacological or other effect of the biological product, when used under adequate directions, for use and warnings against unsafe use, will serve a clinically significant function in the diagnosis, cure, mitigation, treatment, or prevention of disease in man. Proof of effectiveness shall consist of controlled clinical investigations as defined in §314.126 of this chapter, unless this requirement is waived on the basis of a showing that it is not reasonably applicable to the biological product or essential to the validity of the investigation, and that an alternative method of investigation is adequate to substantiate effectiveness. Alternate methods, such as serological response evaluation in clinical studies and appropriate animal and other laboratory assay evaluations may be adequate to substantiate effectiveness where a previously accepted correlation between data generated in this way and clinical effectiveness already exists. Investigations may be corroborated by partially controlled or uncontrolled studies, documented clinical studies by qualified experts, and reports of significant human experience during marketing. Isolated case reports, random experience, and reports lacking the details

which permit scientific evaluation will not be considered.

(3) The benefit-to-risk ratio of a biological product shall be considered in determining safety and effectiveness.

(4) A biological product may combine two or more safe and effective active components: (i) When each active component makes a contribution to the claimed effect or effects; (ii) when combining of the active ingredients does not decrease the purity, potency, safety, or effectiveness of any of the individual active components; and (iii) if the combination, when used under adequate directions for use and warnings against unsafe use, provides rational concurrent preventive therapy or treatment for a significant proportion of the target population.

(5) Labeling shall be clear and truthful in all respects and may not be false or misleading in any particular. It shall comply with section 351 of the Public Health Service Act and sections 502 and 503 of the Federal Food, Drug, and Cosmetic Act, and in particular with the applicable requirements of §§ 610.60 through 610.65 and subpart D of part 201 of this chapter.

(e) *Advisory review panel report to the Commissioner.* An advisory review panel shall submit to the Commissioner of Food and Drugs a report containing the panel's conclusions and recommendations with respect to the biological products falling within the category covered by the panel. Included within this report shall be:

(1) A statement which designates those biological products determined by the panel to be safe and effective and not misbranded. This statement may include any condition relating to active components, labeling, tests required prior to release of lots, product standards, or other conditions necessary or appropriate for their safety and effectiveness.

(2) A statement which designates those biological products determined by the panel to be unsafe or ineffective, or to be misbranded. The statement shall include the panel's reasons for each such determination.

(3) A statement which designates those biological products determined by the panel not to fall within either paragraph (e) (1) or (2) of this section on the basis of the panel's conclusion that the available data are insufficient to classify such biological products, and for which further testing is therefore required. The report shall recommend with as must 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

[2] As of November 4, 1982, the provisions under paragraphs (e)(3) and (f)(3) of this section for the interim marketing of certain biological products pending completion of additional studies have been superseded by the review and reclassification procedures under § 601.26 of this chapter. The superseded text is included for the convenience of the user only.

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.

[2] As of November 4, 1982, the provisions under paragraphs (e)(3) and (f)(3) of this section for the interim marketing of certain biological products pending completion of additional studies have been superseded by the review and reclassification procedures under § 601.26 of this chapter. The superseded text is included for the convenience of the user only.

(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.

[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]

§ 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]

§ 601.27 Pediatric studies.

(a) *Required assessment.* Except as provided in paragraphs (b), (c), and (d) of this section, each application for a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration shall contain data that are adequate to assess the safety and effectiveness of the

product for the claimed indications in all relevant pediatric subpopulations, and to support dosing and administration for each pediatric subpopulation for which the product is safe and effective. Where the course of the disease and the effects of the product are similar in adults and pediatric patients, FDA may conclude that pediatric effectiveness can be extrapolated from adequate and well-controlled effectiveness studies in adults, usually supplemented with other information in pediatric patients, such as pharmacokinetic studies. In addition, studies may not be needed in each pediatric age group, if data from one age group can be extrapolated to another. Assessments required under this section for a product that represents a meaningful therapeutic benefit over existing treatments must be carried out using appropriate formulations for the age group(s) for which the assessment is required.

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

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

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

(2) *Full waiver.* An applicant may request a waiver of the requirements of paragraph (a) of this section if the applicant certifies that:

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

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

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

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

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

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

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

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

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

(5) *Definition of "meaningful therapeutic benefit".* For purposes of this section, a product will be considered to offer a meaningful therapeutic benefit over existing therapies if FDA estimates that:

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

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

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

[63 FR 66671, Dec. 2, 1998]

§ 601.28 Annual reports of postmarketing pediatric studies.

Sponsors of licensed biological products shall submit the following information each year within 60 days of the anniversary date of approval of 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]

§ 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

SOURCE: 64 FR 26668, May 17, 1999, unless otherwise noted.

§ 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.

§ 601.31 Definition.

For purposes of this part, *diagnostic radiopharmaceutical* means:

(a) An article that is intended for use in the diagnosis or monitoring of a disease or a manifestation of a disease in humans and that exhibits spontaneous disintegration of unstable nuclei with the emission of nuclear particles or photons; or

(b) Any nonradioactive reagent kit or nuclide generator that is intended to be used in the preparation of such article as defined in paragraph (a) of this section.

§ 601.32 General factors relevant to safety and effectiveness.

FDA's determination of the safety and effectiveness of a diagnostic radiopharmaceutical includes consideration of the following:

(a) The proposed use of the diagnostic radiopharmaceutical in the practice of medicine;

(b) The pharmacological and toxicological activity of the diagnostic radiopharmaceutical (including any carrier or ligand component of the diagnostic radiopharmaceutical); and

(c) The estimated absorbed radiation dose of the diagnostic radiopharmaceutical.

§ 601.33 Indications.

(a) For diagnostic radiopharmaceuticals, the categories of proposed indications for use include, but are not limited to, the following:

(1) Structure delineation;

(2) Functional, physiological, or biochemical assessment;

(3) Disease or pathology detection or assessment; and

(4) Diagnostic or therapeutic patient management.

(b) Where a diagnostic radiopharmaceutical is not intended to provide disease-specific information, the proposed indications for use may refer to a biochemical, physiological, anatomical, or pathological process or to more than one disease or condition.

§ 601.34 Evaluation of effectiveness.

(a) The effectiveness of a diagnostic radiopharmaceutical is assessed by evaluating its ability to provide useful clinical information related to its proposed indications for use. The method of this evaluation varies depending upon the proposed indication(s) and may use one or more of the following criteria:

(1) The claim of structure delineation is established by demonstrating in a defined clinical setting the ability to locate anatomical structures and to characterize their anatomy.

(2) The claim of functional, physiological, or biochemical assessment is established by demonstrating in a defined clinical setting reliable measurement of function(s) or physiological, biochemical, or molecular process(es).

(3) The claim of disease or pathology detection or assessment is established by demonstrating in a defined clinical setting that the diagnostic radiopharmaceutical has sufficient accuracy in identifying or characterizing the disease or pathology.

(4) The claim of diagnostic or therapeutic patient management is established by demonstrating in a defined clinical setting that the test is useful in diagnostic or therapeutic patient management.

(5) For a claim that does not fall within the indication categories identified in § 601.33, the applicant or sponsor should consult FDA on how to establish the effectiveness of the diagnostic radiopharmaceutical for the claim.

(b) The accuracy and usefulness of the diagnostic information is determined by comparison with a reliable assessment of actual clinical status. A reliable assessment of actual clinical status may be provided by a diagnostic standard or standards of demonstrated accuracy. In the absence of such diagnostic standard(s), the actual clinical status must be established in another manner, e.g., patient followup.

§ 601.35 Evaluation of safety.

(a) Factors considered in the safety assessment of a diagnostic radiopharmaceutical include, among others, the following:

(1) The radiation dose;

(2) The pharmacology and toxicology of the radiopharmaceutical, including any radionuclide, carrier, or ligand;

(3) The risks of an incorrect diagnostic determination;

(4) The adverse reaction profile of the drug;

(5) Results of human experience with the radiopharmaceutical for other uses; and

(6) Results of any previous human experience with the carrier or ligand of the radiopharmaceutical when the same chemical entity as the carrier or ligand has been used in a previously studied product.

(b) The assessment of the adverse reaction profile includes, but is not limited to, an evaluation of the potential of the diagnostic radiopharmaceutical, including the carrier or ligand, to elicit the following:

(1) Allergic or hypersensitivity responses,

(2) Immunologic responses,

(3) Changes in the physiologic or biochemical function of the target and nontarget tissues, and

(4) Clinically detectable signs or symptoms.

(c)(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

SOURCE: 57 FR 58959, Dec. 11, 1992, unless otherwise noted.

§ 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).

§ 601.41 Approval based on a surrogate endpoint or on an effect on a clinical endpoint other than survival or irreversible morbidity.

FDA may grant marketing approval for a biological product on the basis of adequate and well-controlled clinical trials establishing that the biological product has an effect on a surrogate endpoint that is reasonably likely, based on epidemiologic, therapeutic, pathophysiologic, or other evidence, to predict clinical benefit or on the basis of an effect on a clinical endpoint other than survival or irreversible morbidity. Approval under this section will be subject to the requirement that the applicant study the biological product further, to verify and describe its clinical benefit, where there is uncertainty as to the relation of the surrogate endpoint to clinical benefit, or of the observed clinical benefit to ultimate outcome. Postmarketing studies would usually be studies already underway.

When required to be conducted, such studies must also be adequate and well-controlled. The applicant shall carry out any such studies with due diligence.

§ 601.42 Approval with restrictions to assure safe use.

(a) If FDA concludes that a biological product shown to be effective can be safely used only if distribution or use is restricted, FDA will require such postmarketing restrictions as are needed to assure safe use of the biological product, such as:

(1) Distribution restricted to certain facilities or physicians with special training or experience; or

(2) Distribution conditioned on the performance of specified medical procedures.

(b) The limitations imposed will be commensurate with the specific safety concerns presented by the biological product.

§ 601.43 Withdrawal procedures.

(a) For biological products approved under § 601.41 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]

§ 601.44 Postmarketing safety reporting.

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

§ 601.45 Promotional materials.

For biological products being considered for approval under this subpart, unless otherwise informed by the agency, applicants must submit to the agency for consideration during the preapproval review period copies of all promotional materials, including promotional labeling as well as advertisements, intended for dissemination or publication within 120 days following marketing approval. After 120 days following marketing approval, unless otherwise informed by the agency, the applicant must submit promotional materials at least 30 days prior to the intended time of initial dissemination of the labeling or initial publication of the advertisement.

§ 601.46 Termination of requirements.

If FDA determines after approval that the requirements established in § 601.42, § 601.43, or § 601.45 are no longer necessary for the safe and effective use of a biological product, it will so notify the applicant. Ordinarily, for biological products approved under § 601.41, these requirements will no longer apply when FDA determines that the required postmarketing study verifies and describes the biological product's clinical benefit and the biological product would be appropriate for approval under traditional procedures. For biological products approved under § 601.42, the restrictions would no longer apply when FDA determines that safe use of the biological product can be assured through appropriate labeling. FDA also retains the discretion to remove specific postapproval requirements upon review of a petition submitted by the sponsor in accordance with § 10.30.

Subpart F—Confidentiality of Information

§ 601.50 Confidentiality of data and information in an investigational new drug notice for a biological product.

(a) The existence of an IND notice for a biological product will not be disclosed by the Food and Drug Administration unless it has previously been publicly disclosed or acknowledged.

(b) The availability for public disclosure of all data and information in an IND file for a biological product shall be handled in accordance with the provisions established in § 601.51.

(c) Notwithstanding the provisions of § 601.51, the Food and Drug Administration shall disclose upon request to an individual on whom an investigational biological product has been used a copy of any adverse reaction report relating to such use.

[39 FR 44656, Dec. 24, 1974]

§ 601.51 Confidentiality of data and information in applications for biologics licenses.

(a) For purposes of this section the biological product file includes all data and information submitted with or incorporated by reference in any application for a biologics license, IND's incorporated into any such application, master files, and other related submissions. The availability for public disclosure of any record in the biological product file shall be handled in accordance with the provisions of this section.

(b) The existence of a biological product file will not be disclosed by the Food and Drug Administration before a biologics license application has been approved unless it has previously been publicly disclosed or acknowledged. The 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

SOURCE: 65 FR 64618, Oct. 30, 2000, unless otherwise noted.

§ 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

SOURCE: 67 FR 37996, May 31, 2002, unless otherwise noted.

§ 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.

§ 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.

§ 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]

§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.

§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.

§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.

PART 606—CURRENT GOOD MANUFACTURING PRACTICE FOR BLOOD AND BLOOD COMPONENTS

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606.60 Equipment.

AUTHORITY: 21 U.S.C. 321, 331, 351, 352, 355, 360, 360j, 371, 374; 42 U.S.C. 216, 262, 263a, 264.

SOURCE: 40 FR 53532, Nov. 18, 1975, unless otherwise noted.

Subpart A—General Provisions

§ 606.3 Definitions.

As used in this part:

(a) *Blood* means whole blood collected from a single donor and processed either for transfusion or further manufacturing.

(b) *Unit* means the volume of blood or one of its components in a suitable volume of anticoagulant obtained from a single collection of blood from one donor.

(c) *Component* means that part of a single-donor's blood separated by physical or mechanical means.

(d) *Plasma for further manufacturing* means that liquid portion of blood separated and used as material to prepare another product.

(e) *Plasmapheresis* means the procedure in which blood is removed from the donor, the plasma is separated from the formed elements and at least the red blood cells are returned to the donor.

(f) *Plateletpheresis* means the procedure in which blood is removed from a donor, a platelet concentrate is separated, and the remaining formed elements are returned to the donor along with a portion of the residual plasma.

(g) *Leukapheresis* means the procedure in which blood is removed from the donor, a leukocyte concentrate is separated, and the remaining formed elements and residual plasma are returned to the donor.

(h) *Facilities* means any area used for the collection, processing, compatibility testing, storage or distribution of blood and blood components.

(i) *Processing* means any procedure employed after collection, and before or after compatibility testing of blood, and includes the identification of a unit of donor blood, the preparation of components from such unit of donor blood, serological testing, labeling and associated recordkeeping.

(j) *Compatibility testing* means the procedures performed to establish the matching of a donor's blood or blood components with that of a potential recipient.

(k) *Distributed* means:

(1) The blood or blood components have left the control of the licensed manufacturer, unlicensed registered blood establishment, or transfusion service; or

(2) The licensed manufacturer has provided Source Plasma or any other blood component for use in the manufacture of a licensed biological product.

(l) *Control* means having responsibility for maintaining the continued safety, purity, and potency of the product and for compliance with applicable product and establishment standards, and for compliance with current good manufacturing practices.

[40 FR 53532, Nov. 18, 1975, as amended at 64 FR 45370, Aug. 19, 1999; 65 FR 66635, Nov. 7, 2000; 66 FR 1835, Jan. 10, 2001; 66 FR 40889, Aug. 6, 2001; 72 FR 45886, Aug. 16, 2007]

Subpart B—Organization and Personnel

§ 606.20 Personnel.

(a) [Reserved]

(b) The personnel responsible for the collection, processing, compatibility testing, storage or distribution of blood or blood components shall be adequate in number, educational background, training and experience, including professional training as necessary, or combination thereof, to assure competent performance of their assigned functions, and to ensure that the final product has the safety, purity, potency, identity and effectiveness it purports or is represented to possess. All personnel shall have capabilities commensurate with their assigned functions, a thorough understanding of the procedures or control operations they perform, the necessary training or experience, and adequate information concerning the application of pertinent provisions of this part to their respective functions.

(c) Persons whose presence can adversely affect the safety and purity of the products shall be excluded from areas where the collection, processing, compatibility testing, storage or distribution of blood or blood components is conducted.

[40 FR 53532, Nov. 18, 1975, as amended at 49 FR 23833, June 8, 1984; 55 FR 11014, Mar. 26, 1990; 62 FR 53538, Oct. 15, 1997]

Subpart C—Plant and Facilities

§ 606.40 Facilities.

Facilities shall be maintained in a clean and orderly manner, and shall be of suitable size, construction and location to facilitate adequate cleaning, maintenance and proper operations. The facilities shall:

(a) Provide adequate space for the following when applicable:

(1) Private and accurate examinations of individuals to determine their suitability as blood donors.

(2) The withdrawal of blood from donors with minimal risk of contamination, or exposure to activities and equipment unrelated to blood collection.

(3) The storage of blood or blood components pending completion of tests.

(4) The quarantine storage of blood or blood components in a designated location pending repetition of those tests that initially gave questionable serological results.

(5) The storage of finished products prior to distribution.

(6) The quarantine storage, handling and disposition of products and reagents not suitable for use.

(7) The orderly collection, processing, compatibility testing, storage and distribution of blood and blood components to prevent contamination.

(8) The adequate and proper performance of all steps in plasmapheresis, plateletpheresis and leukapheresis procedures.

(9) The orderly conduction of all packaging, labeling and other finishing operations.

(b) Provide adequate lighting, ventilation and screening of open windows and doors.

(c) Provide adequate, clean, and convenient handwashing facilities for personnel, and adequate, clean, and convenient toilet facilities for donors and personnel. Drains shall be of adequate size and, where connected directly to a sewer, shall be equipped with traps to prevent back-siphonage.

(d) Provide for safe and sanitary disposal for the following:

(1) Trash and items used during the collection, processing and compatibility testing of blood and blood components.

(2) Blood and blood components not suitable for use or distribution.

Subpart D—Equipment

§ 606.60 Equipment.

(a) Equipment used in the collection, processing, compatibility testing, storage and distribution of blood and blood components shall be maintained in a clean and orderly manner and located so as to facilitate cleaning and maintenance. The equipment shall be observed, standardized and calibrated on a regularly scheduled basis as prescribed in the Standard Operating Procedures Manual and shall perform in the manner for which it was designed so as to assure compliance with the official requirements prescribed in this chapter for blood and blood products.

(b) Equipment that shall be observed, standardized and calibrated with at least the following frequency, include but are not limited to:

Equipment	Performance check	Frequency	Frequency of calibration
Temperature recorder	Compare against thermometer	Daily	As necessary.
Refrigerated centrifuge	Observe speed and temperature	Each day of use	Do.
Hematocrit centrifuge			Standardize before initial use, after repairs or adjustments, and annually. Timer every 3 mo.
General lab centrifuge			Tachometer every 6 mo.
Automated blood-typing machine.	Observe controls for correct results	Each day of use.	
Hemoglobinometer	Standardize against cyanmethemoglobin standard.	do.	
Refractometer	Standardize against distilled water	do.	
Blood container scale	Standardize against container of known weight.	do	As necessary.
Water bath	Observe temperature	do	Do.
Rh view box	do	do	Do.
Autoclave	do	Each time of use	Do.
Serologic rotators	Observe controls for correct results	Each day of use	Speed as necessary.
Laboratory thermometers.			Before initial use.
Electronic thermometers			Monthly.
Vacuum blood agitator	Observe weight of the first container of blood filled for correct results.	Each day of use	Standardize with container of known mass or volume before initial use, and after repairs or adjustments.

(c) Equipment employed in the sterilization of materials used in blood collection or for disposition of contaminated products shall be designed, maintained and utilized to ensure the destruction of contaminating microorganisms. The effectiveness of the sterilization procedure shall be no less than that achieved by an attained temperature of 121.5 °C (251 °F) maintained for 20 minutes by saturated steam or by an attained temperature of 170 °C (338 °F) maintained for 2 hours with dry heat.

[40 FR 53532, Nov. 18, 1975; 40 FR 55849, Dec. 2, 1975, as amended at 45 FR 9261, Feb. 12, 1980; 57 FR 11263, Apr. 2, 1992; 57 FR 12862, Apr. 13, 1992]

§ 606.65 Supplies and reagents.

All supplies and reagents used in the collection, processing, compatibility testing, storage and distribution of blood and blood components shall be stored in a safe, sanitary and orderly manner.

(a) All surfaces coming in contact with blood and blood components intended for transfusion shall be sterile, pyrogen-free, and shall not interact with the product in such a manner as to have an adverse effect upon the safety, purity, potency or effectiveness of the product. All final containers and closures for blood and blood components not intended for transfusion shall be clean and free of surface solids and other contaminants.

(b) Each blood collecting container and its satellite container(s), if any, shall be examined visually for damage or evidence of contamination prior to its use and immediately after filling. Such examination shall include inspection for breakage of seals, when indicated, and abnormal discoloration. Where any defect is observed, the container shall not be used, or, if detected after filling, shall be properly discarded.

(c) Representative samples of each lot of the following reagents or solutions shall be tested on a regularly scheduled basis by methods described in the Standard Operating Procedures Manual to determine their capacity to perform as required:

Reagent or solution	Frequency of testing
Anti-human globulin	Each day of use.
Blood grouping reagents	Do.
Lectins	Do.
Antibody screening and reverse grouping cells.	Do.
Hepatitis test reagents	Each run.
Syphilis serology reagents	Do.
Enzymes	Each day of use.

(d) Supplies and reagents that do not bear an expiration date shall be stored in such a manner that the oldest is used first.

(e) Supplies and reagents shall be used in a manner consistent with instructions provided by the manufacturer.

(f) Items that are required to be sterile and come into contact with blood should be disposable whenever possible.

[40 FR 53532, Nov. 18, 1975, as amended at 59 FR 23636, May 6, 1994]

Subpart E [Reserved]

Subpart F—Production and Process Controls

§ 606.100 Standard operating procedures.

(a) In all instances, except clinical investigations, standard operating procedures shall comply with published additional standards in part 640 of this chapter for the products being processed; except that, references in part 640 relating to licenses, licensed establishments and submission of material or data to or approval by the Director, Center for Biologics Evaluation and Research, are not applicable to establishments not subject to licensure under section 351 of the Public Health Service Act.

(b) Written standard operating procedures shall be maintained and shall include all steps to be followed in the collection, processing, compatibility testing, storage, and distribution of blood and blood components for transfusion and further manufacturing purposes. Such procedures shall be available to the personnel for use in the areas where the procedures are performed. The written standard operating procedures shall include, but are not limited to, descriptions of the following, when applicable:

(1) Criteria used to determine donor suitability, including acceptable medical history criteria.

(2) Methods of performing donor qualifying tests and measurements, including minimum and maximum values for a test or procedure when a factor in determining acceptability.

(3) Solutions and methods used to prepare the site of phlebotomy to give maximum assurance of a sterile container of blood.

(4) Method of accurately relating the product(s) to the donor.

(5) Blood collection procedure, including in-process precautions taken to measure accurately the quantity of blood removed from the donor.

(6) Methods of component preparation, including any time restrictions for specific steps in processing.

(7) All tests and repeat tests performed on blood and blood components during manufacturing.

(8) Pretransfusion testing, where applicable, including precautions to be taken to identify accurately the recipient blood samples and crossmatched donor units.

(9) Procedures for investigating adverse donor and recipient reactions.

(10) Storage temperatures and methods of controlling storage temperatures for all blood products and reagents as prescribed in §§ 600.15 and 610.53 of this chapter.

(11) Length of expiration dates, if any, assigned for all final products as prescribed in § 610.53 of this chapter.

(12) Criteria for determining whether returned blood is suitable for reissue.

(13) Procedures used for relating a unit of blood or blood component from the donor to its final disposition.

(14) Quality control procedures for supplies and reagents employed in blood collection, processing and pretransfusion testing.

(15) Schedules and procedures for equipment maintenance and calibration.

(16) Labeling procedures, including safeguards to avoid labeling mixups.

(17) Procedures of plasmapheresis, plateletpheresis, and leukapheresis, if performed, including precautions to be taken to ensure reinfusion of a donor's own cells.

(18) Procedures for preparing recovered plasma, if performed, including details of separation, pooling, labeling, storage, and distribution.

(19) Procedures under §§ 610.46, 610.47, and 610.48 of this chapter:

(i) To identify previously donated blood and blood components from a donor who later tests reactive for evidence of human immunodeficiency virus (HIV) infection or hepatitis C virus (HCV) infection when tested under § 610.40 of this chapter, or when a blood establishment is made aware of other reliable test results or information indicating evidence of HIV or HCV infection;

(ii) To quarantine in-date blood and blood components previously donated by such a donor that are intended for use in another person or further manufacture into injectable products, except pooled components intended solely for further manufacturing into products that are manufactured using validated viral clearance procedures;

(iii) To notify consignees to quarantine in-date blood and blood components previously donated by such a donor intended for use in another person or for further manufacture into injectable products, except pooled components intended solely for further manufacturing into products that are manufactured using validated viral clearance procedures;

(iv) To determine the suitability for release, destruction, or relabeling of quarantined in-date blood and blood components;

(v) To notify consignees of the results of the HIV or HCV testing performed on the donors of such blood and blood components;

(vi) To notify the transfusion recipient, the recipient's physician of record, or the recipient's legal representative that the recipient received blood or blood components at increased risk of transmitting HIV or HCV, respectively.

(20) Procedures for donor deferral as prescribed in §610.41 of this chapter; and procedures for donor notification and autologous donor referring physician notification, including procedures for the appropriate followup if the initial attempt at notification fails, as prescribed in §630.6 of this chapter.

(c) All records pertinent to the lot or unit maintained pursuant to these regulations shall be reviewed before the release or distribution of a lot or unit of final product. The review or portions of the review may be performed at appropriate periods during or after blood collecting, processing, compatibility testing and storing. A thorough investigation, including the conclusions and followup, of any unexplained discrepancy or the failure of a lot or unit to meet any of its specifications shall be made and recorded.

(d) In addition to the requirements of this subpart and in conformity with this section, any facility may utilize current standard operating procedures such as the manuals of the organizations, as long as such specific procedures are consistent with, and at least as stringent as, the requirements contained in this part.

(1) American Association of Blood Banks.

(2) American National Red Cross.

(3) Other organizations or individual blood banks, subject to approval by the Director, Center for Biologics Evaluation and Research.

[40 FR 53532, Nov. 18, 1975, as amended at 49 FR 23833, June 8, 1984; 55 FR 11013, Mar. 26, 1990; 61 FR 47422, Sept. 9, 1996; 64 FR 45370, Aug. 19, 1999; 66 FR 31176, June 11, 2001; 72 FR 48798, Aug. 24, 2007]

§606.110 Plateletpheresis, leukapheresis, and plasmapheresis.

(a) The use of plateletpheresis and leukapheresis procedures to obtain a product for a specific recipient may be at variance with the additional standards for specific products prescribed in this part provided that: (1) A physician has determined that the recipient must be transfused with the leukocytes or platelets from a specific donor, and (2) the procedure is performed under the supervision of a qualified licensed physician who is aware of the health status of the donor, and the physician has certified in writing that the donor's health permits plateletpheresis or leukapheresis.

(b) Plasmapheresis of donors who do not meet the donor requirements of §§640.63, 640.64 and 640.65 of this chapter for the collection of plasma containing rare antibodies shall be permitted only with the prior approval of the Director, Center for Biologics Evaluation and Research.

[40 FR 53532, Nov. 18, 1975, as amended at 49 FR 23833, June 8, 1984; 55 FR 11013, Mar. 26, 1990]

Subpart G—Additional Labeling Standards for Blood and Blood Components

§606.120 Labeling, general requirements.

(a) Labeling operations shall be separated physically or spatially from other operations in a manner adequate to prevent mixups.

(b) The labeling operation shall include the following labeling controls:

(1) Labels shall be held upon receipt, pending review and proofing against an approved final copy, to ensure accuracy regarding identity, content, and conformity with the approved copy.

(2) Each type of label representing different products shall be stored and maintained in a manner to prevent mixups, and stocks of obsolete labels shall be destroyed.

(3) All necessary checks in labeling procedures shall be utilized to prevent errors in translating test results to container labels.

(c) All labeling shall be clear and legible.

[50 FR 35469, Aug. 30, 1985]

§ 606.121 Container label.

(a) The container label requirements are designed to facilitate the use of a uniform container label for blood and blood components intended for use in transfusion or further manufacture by all blood establishments.

(b) The label provided by the collecting facility and the initial processing facility must not be removed, altered, or obscured, except that the label may be altered to indicate the proper name of the product, with any appropriate modifiers and attributes, and other information required to identify accurately the contents of a container after blood components considered finished products have been prepared.

(c) The container label must include the following information, as well as other specialized information as required in this section for specific products:

(1) The proper name of the product in a prominent position, with any appropriate modifiers and attributes.

(2) The name, address, unique facility identifier, and, if a licensed product, the license number of each manufacturer; except the container label for blood and blood components for further manufacture is not required to include a unique facility identifier.

(3) The donor or lot number relating the unit to the donor. If pooled, all donor numbers, all donation numbers, or a pool number that is traceable to each individual unit comprising the pool.

(4)(i) The expiration date, including the day, month, and year, and, if the dating period for the product is 72 hours or less, including any product prepared in a system that might compromise sterility, the hour of expiration.

(ii) If Source Plasma intended for manufacturing into noninjectable products is pooled, the expiration date for the pool is determined from the collection date of the oldest unit in the pool, and the pooling records must show the collection date for each unit in the pool.

(5) For Whole Blood, Plasma, Platelets, and partial units of Red Blood Cells, the volume of the product, accurate to within ±10 percent; or optionally for Platelets, the volume or volume range within reasonable limits.

(6) Where applicable, the name and volume of source material.

(7) The recommended storage temperature (in degrees Celsius).

(8) If the product is intended for transfusion, the statements:

(i) "Rx only."

(ii) "See circular of information for indications, contraindications, cautions, and methods of infusion."

(iii) "Properly identify intended recipient."

(iv) "This product may transmit infectious agents."

(v) The appropriate donor classification statement, *i.e.*, "paid donor" or "volunteer donor," in no less prominence than the proper name of the product.

(A) A paid donor is a person who receives monetary payment for a blood donation.

(B) A volunteer donor is a person who does not receive monetary payment for a blood donation.

(C) Benefits, such as time off from work, membership in blood assurance programs, and cancellation of nonreplacement fees that are not readily convertible to cash, do not constitute monetary payment within the meaning of this paragraph.

(9) If the product is intended for transfusion or as is otherwise appropriate, the ABO group and Rh type of

the donor must be designated conspicuously. For Cryoprecipitated Antihemophiliac Factor (AHF), the Rh type may be omitted. The Rh type must be designated as follows:

(i) If the test using Anti-D Blood Grouping Reagent is positive, the product must be labeled: "Rh positive."

(ii) If the test using Anti-D Blood Grouping Reagent is negative, but the test for weak D (formerly D_u) is positive, the product must be labeled: "Rh positive."

(iii) If the test using Anti-D Blood Grouping Reagent is negative and the test for weak D (formerly D_u) is negative, the product must be labeled: "Rh negative."

(10) If the product is not intended for transfusion, a statement as applicable: "Caution: For Manufacturing Use Only," or "Caution: For Use in Manufacturing Noninjectable Products Only," or other cautionary statement as approved by the Director, Center for Biologics Evaluation and Research (CBER).

(11) If the product is intended for further manufacturing use, a statement listing the results of all the tests for communicable disease agents required under § 610.40 of this chapter for which the donation has been tested and found negative; except that the container label for Source Plasma is not required to list the negative results of serological syphilis testing under §§ 610.40(i) and 640.65(b) of this chapter.

(12) The blood and blood components must be labeled in accordance with § 610.40 of this chapter, when the donation is tested and demonstrates evidence of infection due to a communicable disease agent(s).

(13) The container label of blood or blood components intended for transfusion must bear encoded information in a format that is machine-readable and approved for use by the Director, CBER.

(i) *Who is subject to this machine-readable requirement?* All blood establishments that manufacture, process, repack, or relabel blood or blood components intended for transfusion and regulated under the Federal Food, Drug, and Cosmetic Act or the Public Health Service Act.

(ii) *What blood products are subject to this machine-readable requirement?* All blood and blood components intended for transfusion are subject to the machine-readable information label requirement in this section.

(iii) *What information must be machine-readable?* Each label must have machine-readable information that contains, at a minimum:

(A) A unique facility identifier;

(B) Lot number relating to the donor;

(C) Product code; and

(D) ABO and Rh of the donor, except as described in paragraphs (c)(9) and (i)(5) of this section.

(iv) *How must the machine-readable information appear?* The machine-readable information must:

(A) Be unique to the blood or blood component;

(B) Be surrounded by sufficient blank space so that the machine-readable information can be scanned correctly; and

(C) Remain intact under normal conditions of use.

(v) *Where does the machine-readable information go?* The machine-readable information must appear on the label of any blood or blood component which is or can be transfused to a patient or from which the blood or blood component can be taken and transfused to a patient.

(d) Unless otherwise approved by the Director, CBER, the container label for blood and blood components intended for transfusion must be white and print must be solid black, with the following additional exceptions:

(1) The ABO and Rh blood groups must be printed as follows:

(i) Rh positive: Use black print on white background and use solid black or other solid color for ABO.

(ii) Rh negative: Use white print on black background for Rh and use black outline on a white background for ABO.

(2) The proper name of the product, with any appropriate modifiers and attributes, the donor classification statement, and the statement "properly identify intended recipient" may be printed in solid red or in solid black.

(3) The following color scheme may be used for differentiating ABO Blood groups:

Blood group	Color of label
O	Blue
A	Yellow
B	Pink
AB	White

(4) Special labels, such as those described in paragraphs (h) and (i) of this section, may be color-coded.

(e) Container label requirements for particular products or groups of products.

(1) Whole Blood labels must include:

(i) The name of the applicable anticoagulant approved for use by the Director, CBER.

(ii) The volume of anticoagulant.

(iii) If tests for unexpected antibodies are positive, blood intended for transfusion must be labeled: "Contains (name of antibody)."

(2) Except for frozen, deglycerolized, or washed Red Blood Cell products, Red Blood Cell labels must include:

(i) The type of anticoagulant, and if applicable, the volume of Whole Blood and type of additive solution, with which the product was prepared.

(ii) If tests for unexpected antibodies are positive and the product is intended for transfusion, the statement: "Contains (name of antibody)."

(3) If tests for unexpected antibodies are positive, Plasma intended for transfusion must be labeled: "Contains (name of antibody)."

(4) Recovered plasma labels must include:

(i) In lieu of an expiration date, the date of collection of the oldest material in the container.

(ii) For recovered plasma not meeting the requirements for manufacture into licensable products, the statement: "Not for Use in Products Subject to License Under Section 351 of the Public Health Service Act."

(iii) The type of anticoagulant with which the product was prepared.

(5) Source Plasma labels must include the following information:

(i) The cautionary statement, as specified in paragraph (c)(10) of this section, must follow the proper name with any appropriate modifiers and attributes and be of similar prominence as the proper name.

(ii) The statement "Store at −20 °C or colder," provided, that where plasma is intended for manufacturing into noninjectable products, this statement may be replaced by a statement of the temperature appropriate for manufacture of the final product to be prepared from the plasma.

(iii) The total volume or weight of plasma and total quantity and type of anticoagulant used.

(iv) When plasma collected from a donor is reactive for a serologic test for syphilis, a statement that the plasma is reactive and must be used only for the manufacturing of positive control reagents for the serologic test for syphilis.

(v) Source Plasma diverted for Source Plasma Salvaged must be relabeled "Source Plasma Salvaged" as prescribed in §640.76 of this chapter. Immediately following the proper name of the product, with any appropriate modifiers and attributes, the labeling must prominently state as applicable, "STORAGE TEMPERATURE EXCEEDED −20 °C" or "SHIPPING TEMPERATURE EXCEEDED −5 °C."

(vi) A statement as to whether the plasma was collected from normal donors, or from donors in specific collection programs approved by the Director, CBER. In the case of specific collection programs, the label must state the defining characteristics of the plasma. In the case of immunized donors, the label must state the immunizing antigen.

(f) Blood and blood components determined to be unsuitable for transfusion must be prominently labeled "NOT FOR TRANSFUSION," and the label must state the reason the unit is considered unsuitable. The provision does not apply to blood and blood components intended solely for further manufacture.

(g) [Reserved]

(h) The following additional information must appear on the label for blood and blood components shipped in an emergency prior to completion of required tests, in accordance with §610.40(g) of this chapter:

(1) The statement: "FOR EMERGENCY USE ONLY BY ____."

(2) Results of any tests prescribed under §§610.40 and 640.5(a), (b), or (c) of this chapter completed before shipment.

(3) Indication of any tests prescribed under §§ 610.40 and 640.5(a), (b), or (c) of this chapter not completed before shipment.

(i) The following additional information must appear on the label for blood and blood components intended for autologous transfusion:

(1) Information adequately identifying the patient, *e.g.*, name, date of birth, hospital, and identification number.

(2) Date of donation.

(3) The statement: "AUTOLOGOUS DONOR."

(4) The ABO and Rh blood group and type, except as provided in paragraph (c)(9) of this section.

(5) Each container of blood and blood component intended for autologous use and obtained from a donor who fails to meet any of the donor suitability requirements under § 640.3 of this chapter or who is reactive to or positive for one or more tests for evidence of infection due to communicable disease agents under § 610.40 of this chapter must be prominently and permanently labeled "FOR AUTOLOGOUS USE ONLY" and as otherwise required under § 610.40 of this chapter. Such units also may have the ABO and Rh blood group and type on the label.

(6) Units of blood and blood components originally intended for autologous use, except those labeled as prescribed under paragraph (i)(5) of this section, may be issued for allogeneic transfusion provided the container label complies with all applicable provisions of paragraphs (b) through (e) of this section. In such case, the special label required under paragraphs (i)(1), (i)(2), and (i)(3) of this section must be removed or otherwise obscured.

(j) A tie-tag attached to the container may be used for providing the information required by paragraphs (e)(1)(iii), (e)(2)(ii), and (e)(3), (h), or (i)(1), (i)(2), and (i)(3) of this section.

[77 FR 16, Jan. 3, 2012]

§ 606.122 Circular of information.

A circular of information must be available for distribution if the product is intended for transfusion. The circular of information must provide adequate directions for use, including the following information:

(a) Instructions to mix the product before use.

(b) Instructions to use a filter in the administration equipment.

(c) The statement "Do Not Add Medications" or an explanation concerning allowable additives.

(d) A description of the product, its source, and preparation, including the name and proportion of the anticoagulant used in collecting the Whole Blood from each product is prepared.

(e) A statement that the product was prepared from blood that was found negative when tested for communicable disease agents, as required under § 610.40 of this chapter (include each test that was performed).

(f) The statement: "Warning: The risk of transmitting infectious agents is present. Careful donor selection and available laboratory tests do not eliminate the hazard."

(g) The names of cryoprotective agents and other additives that may still be present in the product.

(h) The names and results of all tests performed when necessary for safe and effective use.

(i) The use of the product, indications, contradications, side effects and hazards, dosage and administration recommendations.

(j) [Reserved]

(k) For Red Blood Cells, the circular of information must contain:

(1) Instructions to administer a suitable plasma volume expander if Red Blood Cells are substituted when Whole Blood is the indicated product.

(2) A warning not to add Lactated Ringer's Injection U.S.P. solution to Red Blood Cell products.

(l) For Platelets, the circular of information must contain:

(1) The approximate volume of plasma from which a sample unit of Platelets is prepared.

(2) Instructions to begin administration as soon as possible, but not more than 4 hours after entering the container.

(m) For Plasma, the circular of information must contain:

(1) A warning against further processing of the frozen product if there is evidence of breakage or thawing.

(2) Instructions to thaw the frozen product at a temperature appropriate for the product.

(3) When applicable, instructions to begin administration of the product within a specified time after thawing.

(4) Instructions to administer to ABO-group-compatible recipients.

(5) A statement that this product has the same risk of transmitting infectious agents as Whole Blood; other plasma volume expanders without this risk are available for treating hypovolemia.

(n) For Cryoprecipitated AHF, the circular of information must contain:

(1) A statement that the average potency is 80 or more International Units of antihemophilic factor.

(2) The statement: "Usually contains at least 150 milligrams of fibrinogen"; or, alternatively, the average fibrinogen level determined by assay of representative units.

(3) A warning against further processing of the product if there is evidence of breakage or thawing.

(4) Instructions to thaw the product for no more than 15 minutes at a temperature of between 30 and 37 °C.

(5) Instructions to store at room temperature after thawing and to begin administration as soon as possible but no more than 4 hours after entering the container or after pooling and within 6 hours after thawing.

(6) A statement that 0.9 percent Sodium Chloride Injection U.S.P. is the preferred diluent.

(7) Adequate instructions for pooling to ensure complete removal of all concentrated material from each container.

(8) The statement: "Good patient management requires monitoring treatment responses to Cryoprecipitated AHF transfusions with periodic plasma factor VIII or fibrinogen assays in hemophilia A and hypofibrinogenemic recipients, respectively."

[50 FR 35470, Aug. 30, 1985, as amended at 53 FR 116, Jan. 5, 1988; 64 FR 45371, Aug. 19, 1999; 77 FR 18, Jan. 3, 2012]

Subpart H—Laboratory Controls

§ 606.140 Laboratory controls.

Laboratory control procedures shall include:

(a) The establishment of scientifically sound and appropriate specifications, standards and test procedures to assure that blood and blood components are safe, pure, potent and effective.

(b) Adequate provisions for monitoring the reliability, accuracy, precision and performance of laboratory test procedures and instruments.

(c) Adequate identification and handling of all test samples so that they are accurately related to the specific unit of product being tested, or to its donor, or to the specific recipient, where applicable.

§ 606.151 Compatibility testing.

Standard operating procedures for compatibility testing shall include the following:

(a) A method of collecting and identifying the blood samples of recipients to ensure positive identification.

(b) The use of fresh recipient serum or plasma samples less than 3 days old for all pretransfusion testing if the recipient has been pregnant or transfused within the previous 3 months.

(c) Procedures to demonstrate incompatibility between the donor's cell type and the recipient's serum or plasma type.

(d) A provision that, if the unit of donor's blood has not been screened by a method that will demonstrate agglutinating, coating and hemolytic antibodies, the recipient's cells shall be tested with the donor's serum (minor crossmatch) by a method that will so demonstrate.

(e) Procedures to expedite transfusion in life-threatening emergencies. Records of all such incidents shall be maintained, including complete documentation justifying the emergency action, which shall be signed by a physician.

[40 FR 53532, Nov. 18, 1975, as amended at 64 FR 45371, Aug. 19, 1999; 66 FR 1835, Jan. 10, 2001; 66 FR 40889, Aug. 6, 2001]

Subpart I—Records and Reports

§ 606.160 Records.

(a)(1) Records shall be maintained concurrently with the performance of each significant step in the collection, processing, compatibility testing, storage and distribution of each unit of blood and blood components so that all steps can be clearly traced. All records shall be legible and indelible, and shall identify the person performing the work, include dates of the various entries, show test results as well as the interpretation of the results, show the expiration date assigned to specific products, and be as detailed as necessary to provide a complete history of the work performed.

(2) Appropriate records shall be available from which to determine lot numbers of supplies and reagents used for specific lots or units of the final product.

(b) Records shall be maintained that include, but are not limited to, the following when applicable:

(1) Donor records:

(i) Donor selection, including medical interview and examination and where applicable, informed consent.

(ii) Permanent and temporary deferrals for health reasons including reason(s) for deferral.

(iii) Donor adverse reaction complaints and reports, including results of all investigations and followup.

(iv) Therapeutic bleedings, including signed requests from attending physicians, the donor's disease and disposition of units.

(v) Immunization, including informed consent, identification of the antigen, dosage and route of administration.

(vi) Blood collection, including identification of the phlebotomist.

(vii) Records to relate the donor with the unit number of each previous donation from that donor.

(viii) Records concerning the following activities performed under §§ 610.46, 610.47, and 610.48 of this chapter: Quarantine; consignee notification; testing; notification of a transfusion recipient, the recipient's physician of record, or the recipient's legal representative; and disposition.

(ix) Records of notification of donors deferred or determined not to be suitable for donation, including appropriate followup if the initial attempt at notification fails, performed under § 630.6 of this chapter.

(x) The donor's address provided at the time of donation where the donor may be contacted within 8 weeks after donation.

(xi) Records of notification of the referring physician of a deferred autologous donor, including appropriate followup if the initial notification attempt fails, performed under § 630.6 of this chapter.

(2) Processing records:

(i) Blood processing, including results and interpretation of all tests and retests.

(ii) Component preparation, including all relevant dates and times.

(iii) Separation and pooling of recovered plasma.

(iv) Centrifugation and pooling of source plasma.

(v) Labeling, including initials of the person(s) performing the procedure.

(3) Storage and distribution records:

(i) Distribution and disposition, as appropriate, of blood and blood products.

(ii) Visual inspection of whole blood and red blood cells during storage and immediately before distribution.

(iii) Storage temperature, including initialed temperature recorder charts.

(iv) Reissue, including records of proper temperature maintenance.

(v) Emergency release of blood, including signature of requesting physician obtained before or after release.

(4) Compatibility test records:

(i) Results of all compatibility tests, including crossmatching, testing of patient samples, antibody screening and identification.

(ii) Results of confirmatory testing.

(5) Quality control records:

(i) Calibration and standardization of equipment.

(ii) Performance checks of equipment and reagents.

(iii) Periodic check on sterile technique.

(iv) Periodic tests of capacity of shipping containers to maintain proper temperature in transit.

(v) Proficiency test results.

(6) Transfusion reaction reports and complaints, including records of investigations and followup.

(7) General records:

(i) Sterilization of supplies and reagents prepared within the facility, including date, time interval, temperature and mode.

(ii) Responsible personnel.

(iii) Biological product deviations.

(iv) Maintenance records for equipment and general physical plant.

(v) Supplies and reagents, including name of manufacturer or supplier, lot numbers, expiration date and date of receipt.

(vi) Disposition of rejected supplies and reagents used in the collection, processing and compatibility testing of blood and blood components.

(c) A donor number shall be assigned to each accepted donor, which relates the unit of blood collected to that donor, to his medical record, to any component or blood product from that donor's unit of blood, and to all records describing the history and ultimate disposition of these products.

(d) Records shall be retained for such interval beyond the expiration date for the blood or blood component as necessary to facilitate the reporting of any unfavorable clinical reactions. You must retain individual product records no less than 10 years after the records of processing are completed or 6 months after the latest expiration date for the individual product, whichever is the later date. When there is no expiration date, records shall be retained indefinitely.

(e) A record shall be available from which unsuitable donors may be identified so that products from such individuals will not be distributed.

[40 FR 53532, Nov. 18, 1975, as amended at 61 FR 47422, Sept. 9, 1996; 64 FR 45371, Aug. 19, 1999; 65 FR 66635, Nov. 7, 2000; 66 FR 31176, June 11, 2001; 72 FR 48798, Aug. 24, 2007]

§ 606.165 Distribution and receipt; procedures and records.

(a) Distribution and receipt procedures shall include a system by which the distribution or receipt of each unit can be readily determined to facilitate its recall, if necessary.

(b) Distribution records shall contain information to readily facilitate the identification of the name and address of the consignee, the date and quantity delivered, the lot number of the unit(s), the date of expiration or the date of collection, whichever is applicable, or for crossmatched blood and blood components, the name of the recipient.

(c) Receipt records shall contain the name and address of the collecting facility, date received, donor or lot number assigned by the collecting facility and the date of expiration or the date of collection, whichever is applicable.

§ 606.170 Adverse reaction file.

(a) Records shall be maintained of any reports of complaints of adverse reactions regarding each unit of blood or blood product arising as a result of blood collection or transfusion. A thorough investigation of each reported adverse reaction shall be made. A written report of the investigation of adverse reactions, including conclusions and followup, shall be prepared and maintained as part of the record for that lot or unit of final product by the collecting or transfusing facility. When it is determined that the product was at fault in causing a transfusion reaction, copies of all such written reports shall be forwarded to and maintained by the manufacturer or collecting facility.

(b) When a complication of blood collection or transfusion is confirmed to be fatal, the Director, Office of Compliance and Biologics Quality, CBER, must be notified by telephone, facsimile, express mail, or electronically transmitted mail as soon as possible. A written report of the investigation must be submitted to the Director, Office of Compliance and Biologics Quality, CBER, by mail, facsimile, or electronically transmitted mail (for mailing addresses, see § 600.2 of this chapter), within 7 days after the fatality by the collecting facility in the event of a donor reaction, or by the facility that performed the compatibility tests in the event of a transfusion reaction.

[40 FR 53582, Nov. 18, 1975, as amended at 49 FR 23833, June 8, 1984; 50 FR 35471, Aug. 30, 1985; 55 FR 11014, Mar. 26, 1990; 64 FR 45371, Aug. 19, 1999; 67 FR 9586, Mar. 4, 2002; 77 FR 18, Jan. 3, 2012]

§ 606.171 Reporting of product deviations by licensed manufacturers, unlicensed registered blood establishments, and transfusion services.

(a) *Who must report under this section?* You, a licensed manufacturer of blood and blood components, including Source Plasma; an unlicensed registered blood establishment; or a transfusion service who had control over the product when the deviation occurred, must report under this section. If you arrange for another person to perform a manufacturing, holding, or distribution step, while the product is in your control, that step is performed under your control. You must establish, maintain, and follow a procedure for receiving information from that person on all deviations, complaints, and adverse events concerning the affected product.

(b) *What do I report under this section?* You must report any event, and information relevant to the event, associated with the manufacturing, to include testing, processing, packing, labeling, or storage, or with the holding or distribution, of both licensed and unlicensed blood or blood components, including Source Plasma, if that event meets all the following criteria:

(1) Either:

(i) Represents a deviation from current good manufacturing practice, applicable regulations, applicable standards, or established specifications that may affect the safety, purity, or potency of that product; or

(ii) Represents an unexpected or unforeseeable event that may affect the safety, purity, or potency of that product; and

(2) Occurs in your facility or another facility under contract with you; and

(3) Involves distributed blood or blood components.

(c) *When do I report under this section?* You should report a biological product deviation as soon as possible but you must report at a date not to exceed 45-calendar days from the date you, your agent, or another person who performs a manufacturing, holding, or distribution step under your control, acquire information reasonably suggesting that a reportable event has occurred.

(d) *How do I report under this section?* You must report on Form FDA–3486.

(e) *Where do I report under this section?* You must send the completed Form FDA–3486 to the Director, Office of Compliance and Biologics Quality (HFM–600) (see mailing addresses in § 600.2 of this chapter) by either a paper or electronic filing:

(1) If you make a paper filing, you should identify on the envelope that a BPDR (biological product deviation report) is enclosed; or

(2) If you make an electronic filing, you may submit the completed Form FDA–3486 electronically through CBER's website at *www.fda.gov/cber*.

(f) *How does this regulation affect other FDA regulations?* This part supplements and does not supersede other provisions of the regulations in this chapter. All biological product deviations, whether or not they are required to be reported under this section, should be investigated in accordance with the applicable provisions of parts 211, 606, and 820 of this chapter.

[65 FR 66635, Nov. 7, 2000, as amended at 70 FR 14984, Mar. 24, 2005]

PART 607—ESTABLISHMENT REGISTRATION AND PRODUCT LISTING FOR MANUFACTURERS OF HUMAN BLOOD AND BLOOD PRODUCTS

Subpart A—General Provisions

Sec.

Subpart B—Procedures for Domestic Blood Product Establishments

AUTHORITY: 21 U.S.C. 321, 331, 351, 352, 355, 360, 371, 374, 381, 393; 42 U.S.C. 262, 264, 271.

SOURCE: 40 FR 52788, Nov. 12, 1975, unless otherwise noted.

Subpart A—General Provisions

§ 607.3 Definitions.

(a) The term *act* means the Federal Food, Drug, and Cosmetic Act approved June 25, 1938 (52 Stat. 1040 *et seq.*, as amended, 21 U.S.C. 301–392).

(b) *Blood and blood product* means a drug which consists of human whole blood, plasma, or serum or any product derived from human whole blood, plasma, or serum, hereinafter referred to as "blood product." For the purposes of this part only, blood and blood product also means those products that meet the definition of a device under the Federal Food, Drug, and Cosmetic Act and that are licensed under section 351 of the Public Health Service Act.

(c) *Establishment* means a place of business under one management at one general physical location. The term includes, among others, human blood and plasma donor centers, blood banks, transfusion services, other blood product manufacturers and independent laboratories that engage in quality control and testing for registered blood product establishments.

(d) *Manufacture* means the collection, preparation, processing or compatibility testing by chemical, physical, biological, or other procedures of any blood product which meets the definition of a drug as defined in section 201(g) of the act, and including manipulation, sampling, testing, or control procedures applied to the final product or to any part of the process. The term includes packaging, labeling, repackaging or otherwise changing the container, wrapper, or labeling of any blood product package in furtherance of the distribution of the blood product from the original place of manufacture to the person who makes final delivery or sale to the ultimate consumer.

(e) *Commercial distribution* means any distribution of a blood product except under the investigational use provisions of part 312 of this chapter, but does not include internal or interplant transfer of a bulk product substance between registered establishments within the same parent, subsidiary, and/or affiliate company. For foreign establishments, the term "commercial distribution" shall have the same meaning except that the term shall not include distribution of any blood or blood product that is neither imported nor offered for import into the United States.

(f) *Any material change* includes but is not limited to any change in the name of the blood product, in the quantity or identity of the active ingredient(s) or in the quantity or identity of the inactive ingredient(s) where quantitative listing of all ingredients is required pursuant to § 607.31(a)(2) and any significant change in the labeling of a blood product. Changes that are not significant include changes in arrangement or printing or changes of an editorial nature.

(g) *Bulk product substance* means any substance that is represented for use in a blood product and when used in the manufacturing of a blood product becomes an active ingredient or a finished dosage form of such product.

(h) *Advertising* and *labeling* include the promotional material described in § 202.1(l) (1) and (2) of this chapter, respectively.

(i) The definitions and interpretations contained in sections 201 and 510 of the act shall be applicable to such terms when used in this part 607.

(j) *United States* agent means a person residing or maintaining a place of business in the United States whom a foreign establishment designates as its

agent. This definition excludes mailboxes, answering machines or services, or other places where an individual acting as the foreign establishment's agent is not physically present.

[40 FR 52788, Nov. 12, 1975, as amended at 55 FR 11014, Mar. 26, 1990; 66 FR 59158, Nov. 27, 2001]

§ 607.7 Establishment registration and product listing of blood banks and other firms manufacturing human blood and blood products.

(a) All owners or operators of establishments that engage in the manufacturing of blood products are required to register, pursuant to section 510 of the Federal Food, Drug, and Cosmetic Act. Registration and listing of blood products shall comply with this part. Registration does not permit any blood bank or similar establishment to ship blood products in interstate commerce.

(b) Forms for registration of an establishment are obtainable on request from the Center for Biologics Evaluation and Research (HFM–375) (see mailing addresses in § 600.2 of this chapter), or at any of the Food and Drug Administration district offices.

(c) The completed form should be mailed to the Center for Biologics Evaluation and Research (HFM–375) (see mailing addresses in § 600.2 of this chapter).

[40 FR 52788, Nov. 12, 1975, as amended at 49 FR 23833, June 8, 1984; 55 FR 11014, Mar. 26, 1990; 66 FR 59158, Nov. 27, 2001; 70 FR 14984, Mar. 24, 2005]

Subpart B—Procedures for Domestic Blood Product Establishments

§ 607.20 Who must register and submit a blood product list.

(a) Owners or operators of all establishments, not exempt under section 510(g) of the act or subpart D of this part, that engage in the manufacture of blood products shall register and submit a list of every blood product in commercial distribution (except that registration and listing information may be submitted by the parent, subsidiary, and/or affiliate company for all establishments when operations are conducted at more than one establishment and there exists joint ownership and control among all the establishments). Blood products manufactured, prepared, propagated, compounded, or processed in any State as defined in section 201(a)(1) of the act must be listed whether or not the output of such blood product establishment or any particular blood product so listed enters interstate commerce.

(b) Preparatory to engaging in the manufacture of blood products, owners or operators of establishments who are submitting a biologics license application to manufacture blood products are required to register before the biologics license application is approved.

(c) No registration fee is required. Establishment registration and blood product listing do not constitute an admission or agreement or determination that a blood product is a "drug" within the meaning of section 201(g) of the act.

[40 FR 52788, Nov. 12, 1975, as amended at 64 FR 56452, Oct. 20, 1999; 66 FR 59158, Nov. 27, 2001]

§ 607.21 Times for establishment registration and blood product listing.

The owner or operator of an establishment entering into an operation defined in § 607.3(d) shall register such establishment within 5 days after the beginning of such operation and submit a list of every blood product in commercial distribution at the time. If the owner or operator of the establishment has not previously entered into such operation (defined in § 607.3(d) of this chapter) for which a license is required, registration shall follow within 5 days after the submission of a biologics license application in order to manufacture blood products. Owners or operators of all establishments so engaged shall register annually between November 15 and December 31 and shall update their blood product listing information every June and December.

[40 FR 52788, Nov. 12, 1975, as amended at 64 FR 56453, Oct. 20, 1999]

§ 607.22 How and where to register establishments and list blood products.

(a) The first registration of an establishment shall be on Form FD–2830 (Blood Establishment Registration and Product Listing) obtainable on request

from the Department of Health and Human Services, Food and Drug Administration, Center for Biologics Evaluation and Research (HFM–375), (see mailing addresses in § 600.2 of this chapter), or from Food and Drug Administration district offices. Subsequent annual registration shall also be accomplished on Form FD–2830, which will be furnished by the Food and Drug Administration before November 15 of each year to establishments whose product registration for that year was validated under § 607.35. The completed form shall be mailed to the preceding address before December 31 of that year.

(b) The first list of blood products and subsequent June and December updatings shall be on Form FD–2830, obtainable upon request as described in paragraph (a) of this section.

[66 FR 59158, Nov. 27, 2001, as amended at 70 FR 14984, Mar. 24, 2005]

§ 607.25 Information required for establishment registration and blood product listing.

(a) Form FD–2830 (Blood Establishment Registration and Product Listing) requires furnishing or confirming registration information required by the act. This information includes the name and street address of the establishment, including post office code; all trade names used by the establishment; the kind of ownership or operation (that is, individually owned partnership, or corporation); and the name of the owner or operator of such establishment. The term "name of the owner or operator" shall include in the case of a partnership the name of each partner, and in the case of a corporation the name and title of each corporate officer and director and the name of the State of incorporation. The information required shall be given separately for each establishment, as defined in § 607.3(c).

(b) Form FD–2830 also requires furnishing blood product listing information required by the act as follows:

(1) A list of blood products, including bulk product substances as well as finished dosage forms, by established name as defined in section 502(e) of the act and by proprietary name, which are being manufactured for commercial distribution and which have not been included in any list previously submitted on Form FD–2830 (Blood Establishment Registration and Product Listing) or Form FD–2250 (National Drug Code Directory Input).

(2) For each blood product so listed which is subject to section 351 of the Public Health Service Act, the license number of the manufacturer issued by the Center for Biologics Evaluation and Research, Food and Drug Administration.

(3) For each blood product listed, the registration number of the parent establishment. An establishment not owned, operated, or controlled by another firm or establishment is its own parent establishment.

[40 FR 52788, Nov. 12, 1975, as amended at 49 FR 23833, June 8, 1984; 55 FR 11013, Mar. 26, 1990; 66 FR 59158, Nov. 27, 2001]

§ 607.26 Amendments to establishment registration.

Changes in individual ownership, corporate or partnership structure, location, or blood-product handling activity shall be submitted on Form FDA–2830 (Blood Establishment Registration and Product Listing) as an amendment to registration within 5 days of such changes. Changes in the names of officers and directors of the corporations do not require such amendment but must be shown at time of annual registration.

[40 FR 52788, Nov. 12, 1975, as amended at 66 FR 59158, Nov. 27, 2001]

§ 607.30 Updating blood product listing information.

(a) After submission of the initial blood product listing information, every person who is required to list blood products pursuant to § 607.20 shall submit on Form FD–2830 (Blood Establishment Registration and Product Listing) during each subsequent June and December, or at the discretion of the registrant at the time the change occurs, the following information:

(1) A list of each blood product introduced by the registrant for commercial distribution which has not been included in any list previously submitted. All of the information required by § 607.25(b) shall be provided for each such blood product.

(2) A list of each blood product formerly listed pursuant to § 607.25(b) for which commercial distribution has been discontinued, including for each blood product so listed the identity by established name and proprietary name, and date of discontinuance. It is requested but not required that the reason for discontinuance of distribution be included with this information.

(3) A list of each blood product for which a notice of discontinuance was submitted pursuant to paragraph (a)(2) of this section and for which commercial distribution has been resumed, including for each blood product so listed the identity by established name as defined in section 502(e) of the act and by any proprietary name, the date of resumption, and any other information required by § 607.25(b) not previously submitted.

(4) Any material change in any information previously submitted.

(b) When no changes have occurred since the previously submitted list, no listing information is required.

§ 607.31 Additional blood product listing information.

(a) In addition to the information routinely required by §§ 607.25 and 607.30, the Director of the Center for Biologics Evaluation and Research may require submission of the following information by letter or by FEDERAL REGISTER notice:

(1) For a particular blood product so listed, upon request made by the Director of the Center for Biologics Evaluation and Research for good cause, a copy of all advertisements.

(2) For a particular blood product so listed, upon a finding by the Director of the Center for Biologics Evaluation and Research that it is necessary to carry out the purposes of the act, a quantitative listing of all ingredients.

(3) For each registrant, upon a finding by the Director of the Center for Biologics Evaluation and Research that it is necessary to carry out the purposes of the act, a list of each listed blood product containing a particular ingredient.

(b) [Reserved]

[66 FR 59158, Nov. 27, 2001]

§ 607.35 Notification of registrant; blood product establishment registration number and NDC Labeler Code.

(a) The Director of the Center for Biologics Evaluation and Research will provide to the registrant a validated copy of Form FD–2830 (Blood Establishment Registration and Product Listing) as evidence of registration. This validated copy will be sent to the location shown for the registering establishment, and a copy will be sent to the reporting official if at another address. A permanent registration number will be assigned to each blood product establishment registered in accordance with these regulations.

(b) If a registered blood product establishment has not previously participated in the National Drug Code system, or in the National Health Related Items Code system, the National Drug Code (NDC) numbering system shall be used in assigning the first five numeric characters, otherwise known as the Labeler Code, of the 10-character NDC Code. The Labeler Code identifies the manufacturer.

(c) Although establishment registration and blood product listing are required as described in § 607.20, validation of registration and the assignment of a NDC Labeler Code do not, in themselves, establish that the holder of the registration is legally qualified to deal in such products.

[40 FR 52788, Nov. 12, 1975, as amended at 49 FR 23833, June 8, 1984; 66 FR 59159, Nov. 27, 2001]

§ 607.37 Inspection of establishment registrations and blood product listings.

(a) A copy of the Form FD–2830 (Blood Establishment Registration and Product Listing) filed by the registrant will be available for inspection under section 510(f) of the act, at the Department of Health and Human Services, Food and Drug Administration, Office of Communication, Training and Manufacturers' Assistance (HFM–40), Center for Biologics Evaluation and Research (see mailing addresses in § 600.2 of this chapter). In addition, for domestic firms, the same information will be available for inspection at each of the Food and Drug Administration district

offices for firms within the geographical area of such district office. Upon request and receipt of a self-addressed stamped envelope, verification of registration number, or location of registered establishment will be provided. The following information submitted under the blood product listing requirements is illustrative of the type of information that will be available for public disclosure when it is compiled:

(1) A list of all blood products.

(2) A list of all blood products manufactured by each establishment.

(3) A list of blood products discontinued.

(4) All data or information that has already become a matter of public knowledge.

(b) Requests for information regarding blood establishment registrations and blood product listings should be directed to the Department of Health and Human Services, Food and Drug Administration, Office of Communication, Training and Manufacturers' Assistance (HFM-40), Center for Biologics Evaluation and Research (see mailing addresses in § 600.2 of this chapter).

[40 FR 52788, Nov. 12, 1975, as amended at 49 FR 23833, June 8, 1984; 55 FR 11014, Mar. 26, 1990; 66 FR 59159, Nov. 27, 2001; 70 FR 14984, Mar. 24, 2005]

§ 607.39 Misbranding by reference to establishment registration or to registration number.

Registration of an establishment or assignment of a registration number or assignment of a NDC number does not in any way denote approval of the firm or its products. Any representation that creates an impression of official approval because of establishment registration or possession of registration number or NDC number is misleading and constitutes misbranding.

Subpart C—Procedures for Foreign Blood Product Establishments

§ 607.40 Establishment registration and blood product listing requirements for foreign blood product establishments.

(a) Every foreign establishment shall comply with the establishment registration and blood product listing requirements contained in subpart B of this part, unless exempt under subpart D of this part or unless the blood product enters a foreign trade zone and is re-exported from that foreign trade zone without having entered U. S. commerce.

(b) No blood product may be imported or offered for import into the United States unless it is the subject of a blood product listing as required under subpart B of this part and is manufactured, prepared, propagated, compounded, or processed at a registered foreign establishment; however, this restriction does not apply to a blood product imported or offered for import under the investigational use provisions of part 312 of this chapter or to a blood product imported under section 801(d)(4) of the act. The establishment registration and blood product listing information shall be in the English language.

(c) Each foreign establishment required to register under paragraph (a) of this section shall, as part of the establishment registration and blood product listing, submit the name and address of the establishment and the name of the individual responsible for submitting establishment registration and blood product listing information. Any changes in this information shall be reported to the Food and Drug Administration at the intervals specified for updating establishment registration information in § 607.26 and blood product listing information in § 607.30(a).

(d) Each foreign establishment required to register under paragraph (a) of this section shall submit the name, address, and phone number of its United States agent as part of its initial and updated registration information in accordance with subpart B of this part. Each foreign establishment shall designate only one United States agent.

(1) The United States agent shall reside or maintain a place of business in the United States.

(2) Upon request from FDA, the United States agent shall assist FDA in communications with the foreign establishment, respond to questions concerning the foreign establishment's products that are imported or offered

for import into the United States, and assist FDA in scheduling inspections of the foreign establishment. If the agency is unable to contact the foreign establishment directly or expeditiously, FDA may provide information or documents to the United States agent, and such an action shall be considered to be equivalent to providing the same information or documents to the foreign establishment.

(3) The foreign establishment or the United States agent shall report changes in the United States agent's name, address, or phone number to FDA within 10-business days of the change.

[66 FR 59159, Nov. 27, 2001]

Subpart D—Exemptions

§ 607.65 Exemptions for blood product establishments.

The following classes of persons are exempt from registration and blood product listing in accordance with this part 607 under the provisions of section 510(g)(1), (g)(2), and (g)(3) of the act, or because the Commissioner of Food and Drugs has found, under section 510(g)(5), that such registration is not necessary for the protection of the public health. The exemptions in paragraphs (a), (b), (f), and (g) of this section are limited to those classes of persons located in any State as defined in section 201(a)(1) of the act.

(a) Pharmacies that are operating under applicable local laws regulating dispensing of prescription drugs and that are not manufacturing blood products for sale other than in the regular course of the practice of the profession of pharmacy including the business of dispensing and selling blood products at retail. The supplying by such pharmacies of blood products to a practitioner licensed to administer such blood products for his use in the course of his professional practice or to other pharmacies to meet temporary inventory shortages are not acts which require such pharmacies to register.

(b) Practitioners who are licensed by law to prescribe or administer drugs and who manufacture blood products solely for use in the course of their professional practice.

(c) Persons who manufacture blood products which are not for sale, rather, are solely for use in research, teaching, or analysis, including laboratory samples.

(d) Carriers, by reason of their receipt, carriage, holding, or delivery of blood products in the usual course of business as carriers.

(e) Persons who engage solely in the manufacture of in vitro diagnostic blood products and reagents not subject to licensing under section 351 of the Public Health Service Act (42 U.S.C. 262). This paragraph does not exempt such persons from registration and listing for medical devices required under part 807 of this chapter.

(f) Transfusion services which are a part of a facility that is certified under the Clinical Laboratory Improvement Amendments of 1988 (42 U.S.C. 263a) and 42 CFR part 493 or has met equivalent requirements as determined by the Centers for Medicare and Medicaid Services and which are engaged in the compatibility testing and transfusion of blood and blood components, but which neither routinely collect nor process blood and blood components. The collection and processing of blood and blood components in an emergency situation as determined by a responsible person and documented in writing, therapeutic collection of blood or plasma, the preparation of recovered human plasma for further manufacturing use, or preparation of red blood cells for transfusion are not acts requiring such transfusion services to register.

[40 FR 52788, Nov. 12, 1975, as amended at 43 FR 37997, Aug. 25, 1978; 45 FR 85729, Dec. 30, 1980; 49 FR 34449, Aug. 31, 1984; 66 FR 31162, June 11, 2001; 66 FR 59159, Nov. 27, 2001; 72 FR 45886, Aug. 16, 2007]

PART 610—GENERAL BIOLOGICAL PRODUCTS STANDARDS

Subpart A—Release Requirements

Sec.

AUTHORITY: 21 U.S.C. 321, 331, 351, 352, 353, 355, 360, 360c, 360d, 360h, 360i, 371, 372, 374, 381; 42 U.S.C. 216, 262, 263, 263a, 264.

SOURCE: 38 FR 32056, Nov. 20, 1973, unless otherwise noted.

CROSS REFERENCES: For U.S. Customs Service regulations relating to viruses, serums, and toxins, see 19 CFR 12.21–12.23. For U.S. Postal Service regulations relating to the admissibility to the United States mails see parts 124 and 125 of the Domestic Mail Manual, that is incorporated by reference in 39 CFR part 111.

Subpart A—Release Requirements

§ 610.1 Tests prior to release required for each lot.

No lot of any licensed product shall be released by the manufacturer prior to the completion of tests for conformity with standards applicable to such product. Each applicable test shall be made on each lot after completion of all processes of manufacture which may affect compliance with the standard to which the test applies. The results of all tests performed shall be considered in determining whether or not the test results meet the test objective, except that a test result may be disregarded when it is established that the test is invalid due to causes unrelated to the product.

§ 610.2 Requests for samples and protocols; official release.

(a) *Licensed biological products regulated by CBER.* Samples of any lot of any licensed product together with the protocols showing results of applicable tests, may at any time be required to be sent to the Director, Center for Biologics Evaluation and Research (see mailing addresses in § 600.2 of this chapter). Upon notification by the Director, Center for Biologics Evaluation and Research, a manufacturer shall not distribute a lot of a product until the lot is released by the Director, Center for Biologics Evaluation and Research: *Provided,* That the Director, Center for Biologics Evaluation and Research, shall not issue such notification except when deemed necessary for the safety, purity, or potency of the product.

(b) *Licensed biological products regulated by CDER.* Samples of any lot of any licensed product together with the protocols showing results of applicable tests, may at any time be required to be sent to the Director, Center for Drug Evaluation and Research (see mailing addresses in § 600.2) for official

release. Upon notification by the Director, Center for Drug Evaluation and Research, a manufacturer shall not distribute a lot of a biological product until the lot is released by the Director, Center for Drug Evaluation and Research: *Provided*, That the Director, Center for Drug Evaluation and Research shall not issue such notification except when deemed necessary for the safety, purity, or potency of the product.

[40 FR 31313, July 25, 1975, as amended at 49 FR 23834, June 8, 1984; 50 FR 10941, Mar. 19, 1985; 55 FR 11013 and 11014, Mar. 26, 1990; 67 FR 9587, Mar. 4, 2002; 70 FR 14984, Mar. 24, 2005]

Subpart B—General Provisions

§ 610.9 Equivalent methods and processes.

Modification of any particular test method or manufacturing process or the conditions under which it is conducted as required in this part or in the additional standards for specific biological products in parts 620 through 680 of this chapter shall be permitted only under the following conditions:

(a) The applicant presents evidence, in the form of a license application, or a supplement to the application submitted in accordance with § 601.12(b) or (c), demonstrating that the modification will provide assurances of the safety, purity, potency, and effectiveness of the biological product equal to or greater than the assurances provided by the method or process specified in the general standards or additional standards for the biological product; and

(b) Approval of the modification is received in writing from the Director, Center for Biologics Evaluation and Research or the Director, Center for Drug Evaluation and Research.

[62 FR 39908, July 24, 1997, as amended at 70 FR 14984, Mar. 24, 2005]

§ 610.10 Potency.

Tests for potency shall consist of either in vitro or in vivo tests, or both, which have been specifically designed for each product so as to indicate its potency in a manner adequate to satisfy the interpretation of potency given by the definition in § 600.3(s) of this chapter.

§ 610.11 General safety.

A general safety test for the detection of extraneous toxic contaminants shall be performed on biological products intended for administration to humans. The general safety test is required in addition to other specific tests prescribed in the additional standards for individual products in this subchapter, except that, the test need not be performed on those products listed in paragraph (g) of this section. The general safety test shall be performed as specified in this section, unless: Modification is prescribed in the additional standards for specific products, or variation is approved as a supplement to the product license under § 610.9.

(a) *Product to be tested.* The general safety test shall be conducted upon a representative sample of the product in the final container from every final filling of each lot of the product. If any product is processed further after filling, such as by freeze-drying, sterilization, or heat treatment, the test shall be conducted upon a sample from each filling of each drying chamber run, sterilization chamber, or heat treatment bath.

(b) *Test animals.* Only overtly healthy guinea pigs weighing less than 400 grams each and mice weighing less than 22 grams each shall be used. The animals shall not have been used previously for any test purpose.

(c) *Procedure.* The duration of the general safety test shall be 7 days for both species, except that a longer period may be established for specific products in accordance with § 610.9. Once the manufacturer has established a specific duration of the test period for a specific product, it cannot be varied subsequently, except, in accordance with § 610.9. Each test animal shall be weighed and the individual weights recorded immediately prior to injection and on the last day of the test. Each animal shall be observed every working day. Any animal response including any which is not specific for or expected from the product and which may indicate a difference in its quality

shall be recorded on the day such response is observed. The test product shall be administered as follows:

(1) *Liquid product or freeze-dried product which has been reconstituted as directed on the label.* Inject intraperitoneally 0.5 milliliter of the liquid product or the reconstituted product into each of at least two mice, and 5.0 milliliters of the liquid product or the reconstituted product into each of at least two guinea pigs.

(2) *Freeze-dried product for which the volume of reconstitution is not indicated on the label.* The route of administration, test dose, and diluent shall be as approved in accordance with § 610.9. Administer the test product as approved on at least two mice and at least two guinea pigs.

(3) *Nonliquid products other than freeze-dried product.* The route of administration, test dose, and diluent shall be as in accordance with § 610.9. Dissolve or grind and suspend the product in the approved diluent. Administer the test product as approved on at least two mice and at least two guinea pigs.

(d) *Test requirements.* A safety test is satisfactory if all animals meet all of the following requirements:

(1) They survive the test period.

(2) They do not exhibit any response which is not specific for or expected from the product and which may indicate a difference in its quality.

(3) They weigh no less at the end of the test period than at the time of injection.

(e) *Repeat tests*—(1) *First repeat test.* If a filling fails to meet the requirements of paragraph (d) of this section in the initial test, a repeat test may be conducted on the species which failed the initial test, as prescribed in paragraph (c) of this section. The filling is satisfactory only if each retest animal meets the requirements prescribed in paragraph (d) of this section.

(2) *Second repeat test.* If a filling fails to meet the requirements of the first repeat test, a second repeat test may be conducted on the species which failed the test: *Provided,* That 50 percent of the total number of animals in that species has survived the initial and first repeat tests. The second repeat test shall be conducted as prescribed in paragraph (c) of this section, except that the number of animals shall be twice that used in the first repeat test. The filling is satisfactory only if each second repeat test animal meets the requirements prescribed in paragraph (d) of this section.

(f) [Reserved]

(g) *Exceptions*—(1) The test prescribed in this section need not be performed for Whole Blood, Red Blood Cells, Cryoprecipitated AHF, Platelets, Plasma, or Cellular Therapy Products.

(2) For products other than those identified in paragraph (g)(1) of this section, a manufacturer may request from 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), an exemption from the general safety test. The manufacturer must submit information as part of a biologics license application submission or supplement to an approved biologics license application establishing that because of the mode of administration, the method of preparation, or the special nature of the product a test of general safety is unnecessary to assure the safety, purity, and potency of the product or cannot be performed. The request must include alternate procedures, if any, to be performed. The Director, Center for Biologics Evaluation and Research or the Director, Center for Drug Evaluation and Research, upon finding that the manufacturer's request justifies an exemption, may exempt the product from the general safety test subject to any condition necessary to assure the safety, purity, and potency of the product.

[41 FR 10891, Mar. 15, 1976, as amended at 49 FR 15187, Apr. 18, 1984; 49 FR 23834, June 8, 1984; 50 FR 4133, Jan. 29, 1985; 51 FR 15607, Apr. 25, 1986; 55 FR 11013, Mar. 26, 1990; 59 FR 49351, Sept. 28, 1994; 63 FR 19403, Apr. 20, 1998; 63 FR 41718, Aug. 5, 1998; 68 FR 10160, Mar. 4, 2003; 70 FR 14984, Mar. 24, 2005]

§ 610.11a Inactivated influenza vaccine, general safety test.

For inactivated influenza vaccine, the general safety test shall be conducted in the manner indicated in § 610.11 of this chapter except that, with reference to guinea pigs, the test shall

be satisfied if the product provides satisfactory results using either the subcutaneous or intraperitoneal injection of 5.0 milliliters of inactivated influenza vaccine into each guinea pig. The requirements for general safety for inactivated influenza vaccine shall not be considered to be satisfied unless each lot of influenza vaccine is assayed for endotoxin in comparison to a reference preparation provided by the Food and Drug Administration, and such lot is found to contain no more endotoxin than the reference preparation.

[39 FR 40016, Nov. 13, 1974]

§ 610.12 Sterility.

(a) *The test.* Except as provided in paragraph (h) of this section, manufacturers of biological products must perform sterility testing of each lot of each biological product's final container material or other material, as appropriate and as approved in the biologics license application or supplement for that product.

(b) *Test requirements.* (1) The sterility test must be appropriate to the material being tested such that the material does not interfere with or otherwise hinder the test.

(2) The sterility test must be validated to demonstrate that the test is capable of reliably and consistently detecting the presence of viable contaminating microorganisms.

(3) The sterility test and test components must be verified to demonstrate that the test method can consistently detect the presence of viable contaminating microorganisms.

(c) *Written procedures.* Manufacturers must establish, implement, and follow written procedures for sterility testing that describe, at a minimum, the following:

(1) The sterility test method to be used;

(i) If culture-based test methods are used, include, at a minimum:

(A) Composition of the culture media;

(B) Growth-promotion test requirements; and

(C) Incubation conditions (time and temperature).

(ii) If non-culture-based test methods are used, include, at a minimum:

(A) Composition of test components;

(B) Test parameters, including acceptance criteria; and

(C) Controls used to verify the method's ability to detect the presence of viable contaminating microorganisms.

(2) The method of sampling, including the number, volume, and size of articles to be tested;

(3) Written specifications for the acceptance or rejection of each lot; and

(4) A statement of any other function critical to the particular sterility test method to ensure consistent and accurate results.

(d) *The sample.* The sample must be appropriate to the material being tested, considering, at a minimum:

(1) The size and volume of the final product lot;

(2) The duration of manufacturing of the drug product;

(3) The final container configuration and size;

(4) The quantity or concentration of inhibitors, neutralizers, and preservatives, if present, in the tested material;

(5) For a culture-based test method, the volume of test material that results in a dilution of the product that is not bacteriostatic or fungistatic; and

(6) For a non-culture-based test method, the volume of test material that results in a dilution of the product that does not inhibit or otherwise hinder the detection of viable contaminating microorganisms.

(e) *Verification.* (1) For culture-based test methods, studies must be conducted to demonstrate that the performance of the test organisms and culture media are suitable to consistently detect the presence of viable contaminating microorganisms, including tests for each lot of culture media to verify its growth-promoting properties over the shelf-life of the media.

(2) For non-culture-based test methods, within the test itself, appropriate controls must be used to demonstrate the ability of the test method to continue to consistently detect the presence of viable contaminating microorganisms.

(f) *Repeat test procedures.* (1) If the initial test indicates the presence of microorganisms, the product does not comply with the sterility test requirements unless a thorough investigation

by the quality control unit can ascribe definitively the microbial presence to a laboratory error or faulty materials used in conducting the sterility testing.

(2) If the investigation described in paragraph (f)(1) of this section finds that the initial test indicated the presence of microorganisms due to laboratory error or the use of faulty materials, a sterility test may be repeated one time. If no evidence of microorganisms is found in the repeat test, the product examined complies with the sterility test requirements. If evidence of microorganisms is found in the repeat test, the product examined does not comply with the sterility test requirements.

(3) If a repeat test is conducted, the same test method must be used for both the initial and repeat tests, and the repeat test must be conducted with comparable product that is reflective of the initial sample in terms of sample location and the stage in the manufacturing process from which it was obtained.

(g) *Records.* The records related to the test requirements of this section must be prepared and maintained as required by §§ 211.167 and 211.194 of this chapter.

(h) *Exceptions.* Sterility testing must be performed on final container material or other appropriate material as defined in the approved biologics license application or supplement and as described in this section, except as follows:

(1) This section does not require sterility testing for Whole Blood, Cryoprecipitated Antihemophilic Factor, Platelets, Red Blood Cells, Plasma, Source Plasma, Smallpox Vaccine, Reagent Red Blood Cells, Anti-Human Globulin, and Blood Grouping Reagents.

(2) A manufacturer is not required to comply with the sterility test requirements if the Director of the Center for Biologics Evaluation and Research or the Director of the Center for Drug Evaluation and Research, as appropriate, determines that data submitted in the biologics license application or supplement adequately establish that the route of administration, the method of preparation, or any other aspect of the product precludes or does not necessitate a sterility test to assure the safety, purity, and potency of the product.

[77 FR 26174, May 3, 2012]

§ 610.13 Purity.

Products shall be free of extraneous material except that which is unavoidable in the manufacturing process described in the approved biologics license application. In addition, products shall be tested as provided in paragraphs (a) and (b) of this section.

(a)(1) *Test for residual moisture.* Each lot of dried product shall be tested for residual moisture and shall meet and not exceed established limits as specified by an approved method on file in the biologics license application. The test for residual moisture may be exempted by the Director, Center for Biologics Evaluation and Research or the Director, Center for Drug Evaluation and Research, when deemed not necessary for the continued safety, purity, and potency of the product.

(2) *Records.* Appropriate records for residual moisture under paragraph (a)(1) of this section shall be prepared and maintained as required by the applicable provisions of §§ 211.188 and 211.194 of this chapter.

(b) *Test for pyrogenic substances.* Each lot of final containers of any product intended for use by injection shall be tested for pyrogenic substances by intravenous injection into rabbits as provided in paragraphs (b) (1) and (2) of this section: *Provided,* That notwithstanding any other provision of Subchapter F of this chapter, the test for pyrogenic substances is not required for the following products: Products containing formed blood elements; Cryoprecipitate; Plasma; Source Plasma; Normal Horse Serum; bacterial, viral, and rickettsial vaccines and antigens; toxoids; toxins; allergenic extracts; venoms; diagnostic substances and trivalent organic arsenicals.

(1) *Test dose.* The test dose for each rabbit shall be at least 3 milliliters per kilogram of body weight of the rabbit and also shall be at least equivalent proportionately, on a body weight basis, to the maximum single human dose recommended, but need not exceed 10 milliliters per kilogram of body

weight of the rabbit, except that: (i) Regardless of the human dose recommended, the test dose per kilogram of body weight of each rabbit shall be at least 1 milliliter for immune globulins derived from human blood; (ii) for Streptokinase, the test dose shall be at least equivalent proportionately, on a body weight basis, to the maximum single human dose recommended.

(2) *Test procedure, results, and interpretation; standards to be met.* The test for pyrogenic substances shall be performed according to the requirements specified in United States Pharmacopeia XX.

(3) *Retest.* If the lot fails to meet the test requirements prescribed in paragraph (b)(2) of this section, the test may be repeated once using five other rabbits. The temperature rises recorded for all eight rabbits used in testing shall be included in determining whether the requirements are met. The lot meets the requirements for absence of pyrogens if not more than three of the eight rabbits show individual rises in temperature of 0.6 °C or more, and if the sum of the eight individual maximum temperature rises does not exceed 3.7 °C.

[38 FR 32056, Nov. 20, 1973, as amended at 40 FR 29710, July 15, 1975; 41 FR 10429, Mar. 11, 1976; 41 FR 41424, Sept. 22, 1976; 44 FR 40289, July 10, 1979; 46 FR 62845, Dec. 29, 1981; 49 FR 15187, Apr. 18, 1984; 50 FR 4134, Jan. 29, 1985; 55 FR 28381, July 11, 1990; 64 FR 56453, Oct. 20, 1999; 67 FR 9587, Mar. 4, 2002; 70 FR 14985, Mar. 24, 2005]

§ 610.14 Identity.

The contents of a final container of each filling of each lot shall be tested for identity after all labeling operations shall have been completed. The identity test shall be specific for each product in a manner that will adequately identify it as the product designated on final container and package labels and circulars, and distinguish it from any other product being processed in the same laboratory. Identity may be established either through the physical or chemical characteristics of the product, inspection by macroscopic or microscopic methods, specific cultural tests, or in vitro or in vivo immunological tests.

§ 610.15 Constituent materials.

(a) *Ingredients, preservatives, diluents, adjuvants.* All ingredients used in a licensed product, and any diluent provided as an aid in the administration of the product, shall meet generally accepted standards of purity and quality. Any preservative used shall be sufficiently nontoxic so that the amount present in the recommended dose of the product will not be toxic to the recipient, and in the combination used it shall not denature the specific substances in the product to result in a decrease below the minimum acceptable potency within the dating period when stored at the recommended temperature. Products in multiple-dose containers shall contain a preservative, except that a preservative need not be added to Yellow Fever Vaccine; Poliovirus Vaccine Live Oral; viral vaccines labeled for use with the jet injector; dried vaccines when the accompanying diluent contains a preservative; or to an Allergenic Product in 50 percent or more volume in volume (v/v) glycerin. An adjuvant shall not be introduced into a product unless there is satisfactory evidence that it does not affect adversely the safety or potency of the product. The amount of aluminum in the recommended individual dose of a biological product shall not exceed:

(1) 0.85 milligrams if determined by assay;

(2) 1.14 milligrams if determined by calculation on the basis of the amount of aluminum compound added; or

(3) 1.25 milligrams determined by assay provided that data demonstrating that the amount of aluminum used is safe and necessary to produce the intended effect are submitted to and approved by 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).

(b) *Extraneous protein; cell culture produced vaccines.* Extraneous protein known to be capable of producing allergenic effects in human subjects shall not be added to a final virus medium of cell culture produced vaccines intended for injection. If serum is used at any stage, its calculated concentration in

the final medium shall not exceed 1:1,000,000.

(c) *Antibiotics.* A minimum concentration of antibiotics, other than penicillin, may be added to the production substrate of viral vaccines.

(d) The Director of the Center for Biologics Evaluation and Research or the Director of the Center for Drug Evaluation and Research may approve an exception or alternative to any requirement in this section. Requests for such exceptions or alternatives must be in writing.

[38 FR 32056, Nov. 20, 1973, as amended at 46 FR 51903, Oct. 23, 1981; 48 FR 13025, Mar. 29, 1983; 48 FR 37023, Aug. 16, 1983; 49 FR 23834, June 8, 1984; 50 FR 4134, Jan. 29, 1985; 51 FR 15607, Apr. 25, 1986; 55 FR 11013, Mar. 26, 1990; 70 FR 14985, Mar. 24, 2005; 76 FR 20518, Apr. 13, 2011]

§ 610.16 Total solids in serums.

Except as otherwise provided by regulation, no liquid serum or antitoxin shall contain more than 20 percent total solids.

§ 610.17 Permissible combinations.

Licensed products may not be combined with other licensed products either therapeutic, prophylactic or diagnostic, except as a license is obtained for the combined product. Licensed products may not be combined with nonlicensable therapeutic, prophylactic, or diagnostic substances except as a license is obtained for such combination.

§ 610.18 Cultures.

(a) *Storage and maintenance.* Cultures used in the manufacture of products shall be stored in a secure and orderly manner, at a temperature and by a method that will retain the initial characteristics of the organisms and insure freedom from contamination and deterioration.

(b) *Identity and verification.* Each culture shall be clearly identified as to source strain. A complete identification of the strain shall be made for each new stock culture preparation. Primary and subsequent seed lots shall be identified by lot number and date of preparation. Periodic tests shall be performed as often as necessary to verify the integrity of the strain characteristics and freedom from extraneous organisms. Results of all periodic tests for verification of cultures and determination of freedom from extraneous organisms shall be recorded and retained.

(c) *Cell lines used for manufacturing biological products*—(1) *General requirements.* Cell lines used for manufacturing biological products shall be:

(i) Identified by history;

(ii) Described with respect to cytogenetic characteristics and tumorigenicity;

(iii) Characterized with respect to in vitro growth characteristics and life potential; and

(iv) Tested for the presence of detectable microbial agents.

(2) *Tests.* Tests that are necessary to assure the safety, purity, and potency of a product may be required by the Director, Center for Biologics Evaluation and Research or the Director, Center for Drug Evaluation and Research.

(3) *Applicability.* This paragraph applies to diploid and nondiploid cell lines. Primary cell cultures that are not subcultivated and primary cell cultures that are subsequently subcultivated for only a very limited number of population doublings are not subject to the provisions of this paragraph (c).

(d) *Records.* The records appropriate for cultures under this section shall be prepared and maintained as required by the applicable provisions of §§ 211.188 and 211.194 of this chapter.

[38 FR 32056, Nov. 20, 1973, as amended at 51 FR 44453, Dec. 10, 1986; 55 FR 11013, Mar. 26, 1990; 67 FR 9587, Mar. 4, 2002; 70 FR 14985, Mar. 24, 2005]

Subpart C—Standard Preparations and Limits of Potency

§ 610.20 Standard preparations.

Standard preparations made available by the Center for Biologics Evaluation and Research shall be applied in testing, as follows:

(a) *Potency standards.* Potency standards shall be applied in testing for potency all forms of the following:

ANTIBODIES

Botulism Antitoxin, Type A.
Botulism Antitoxin, Type B.
Botulism Antitoxin, Type E.
Diphtheria Antitoxin.

Histolyticus Antitoxin.
Oedematiens Antitoxin.
Perfringens Antitoxin.
Antipertussis Serum.
Antirabies Serum.
Sordellii Antitoxin.
Staphylococcus Antitoxin.
Tetanus Antitoxin.
Vibrion Septique Antitoxin.

ANTIGENS

Cholera Vaccine, Inaba serotype.
Cholera Vaccine, Ogawa serotype.
Diphtheria Toxin for Schick Test.
Pertussis Vaccine.
Tuberculin, Old.
Tuberculin, Purified Protein Derivative.
Typhoid Vaccine.

BLOOD DERIVATIVE

Thrombin.

(b) *Opacity standard.* The U.S. Opacity Standard shall be applied in estimating the bacterial concentration of all bacterial vaccines. The assigned value of the standard when observed visually is 10 units. The assigned value of the standard when observed with a photometer is (1) 10 units when the wavelength of the filter is 530 millimicrons, (2) 10.6 units when the wavelength of the filter is 650 millimicrons, and (3) 9 units when the wavelength of the filter is 420 millimicrons.

[38 FR 32056, Nov. 20, 1973, as amended at 41 FR 10429, Mar. 11, 1976; 41 FR 18295, May 3, 1976; 49 FR 23834, June 8, 1984; 55 FR 11013, Mar. 26, 1990]

§ 610.21 Limits of potency.

The potency of the following products shall be not less than that set forth below and products dispensed in the dried state shall represent liquid products having the stated limitations.

ANTIBODIES

Diphtheria Antitoxin, 500 units per milliliter.
Tetanus Antitoxin, 400 units per milliliter.
Tetanus Immune Globulin (Human), 250 units of tetanus antitoxin per container.

ANTIGENS

Cholera Vaccine, 8 units each of Inaba and Ogawa serotype antigens per milliliter.
Pertussis Vaccine, 12 units per total human immunizing dose.
Typhoid Vaccine, 8 units per milliliter.

[41 FR 10429, Mar. 11, 1976, as amended at 41 FR 18295, May 3, 1976; 70 FR 75028, Dec. 19, 2005]

Subpart D—Mycoplasma

§ 610.30 Test for *Mycoplasma.*

Except as provided otherwise in this subchapter, prior to clarification or filtration in the case of live virus vaccines produced from in vitro living cell cultures, and prior to inactivation in the case of inactivated virus vaccines produced from such living cell cultures, each virus harvest pool and control fluid pool shall be tested for the presence of *Mycoplasma*, as follows:

Samples of the virus for this test shall be stored either (1) between 2 and 8 °C for no longer than 24 hours, or (2) at −20 °C or lower if stored for longer than 24 hours. The test shall be performed on samples of the viral harvest pool and on control fluid pool obtained at the time of viral harvest, as follows: No less than 2.0 ml. of each sample shall be inoculated in evenly distributed amounts over the surface of no less than 10 plates of at least two agar media. No less than 1.0 ml. of sample shall be inoculated into each of four tubes containing 10 ml. of a semisolid broth medium. The media shall be such as have been shown to be capable of detecting known *Mycoplasma* and each test shall include control cultures of at least two known strains of *Mycoplasma*, one of which must be *M. pneumoniae.* One half of the plates and two tubes of broth shall be incubated aerobically at 36 °C ±1 °C and the remaining plates and tubes shall be incubated anaerobically at 36 °C ±1 °C in an environment of 5–10 percent CO_2 in N_2. Aerobic incubation shall be for a period of no less than 14 days and the broth in the two tubes shall be tested after 3 days and 14 days, at which times 0.5 ml. of broth from each of the two tubes shall be combined and subinoculated on to no less than 4 additional plates and incubated aerobically. Anaerobic incubation shall be for no less than 14 days and the broth in the two tubes shall be tested after 3 days and 14 days, at which times 0.5 ml. of broth from each of the two tubes shall be combined and subinoculated onto no less than four additional plates and incubated anaerobically. All inoculated plates shall be incubated for no less than 14 days, at which time observation for growth of *Mycoplasma* shall be made at a magnification of no less than 300×. If the Dienes Methylene Blue-Azure dye or an equivalent staining procedure is used, no less than a one square cm. plug of the agar shall be excised from the inoculated area and examined for the presence of *Mycoplasma.* The presence of the *Mycoplasma* shall be determined by comparison of the growth obtained from the test samples with that of the control cultures, with respect to typical colonial and microscopic

morphology. The virus pool is satisfactory for vaccine manufacture if none of the tests on the samples show evidence of the presence of *Mycoplasma*.

[38 FR 32056, Nov. 20, 1973, as amended at 63 FR 16685, Apr. 6, 1998]

Subpart E—Testing Requirements for Communicable Disease Agents

§610.40 Test requirements.

(a) *Human blood and blood components.* Except as specified in paragraphs (c) and (d) of this section, you, an establishment that collects blood or blood components, must test each donation of human blood or blood component intended for use in preparing a product, including donations intended as a component of, or used to prepare, a medical device, for evidence of infection due to the following communicable disease agents:

(1) Human immunodeficiency virus, type 1;

(2) Human immunodeficiency virus, type 2;

(3) Hepatitis B virus;

(4) Hepatitis C virus;

(5) Human T-lymphotropic virus, type I; and

(6) Human T-lymphotropic virus, type II.

(b) *Testing using one or more approved screening tests.* To test for evidence of infection due to communicable disease agents designated in paragraph (a) of this section, you must use screening tests that the Food and Drug Administration (FDA) has approved for such use, in accordance with the manufacturer's instructions. You must perform one or more such tests as necessary to reduce adequately and appropriately the risk of transmission of communicable disease.

(c) *Exceptions to testing for allogeneic transfusion or further manufacturing use*—(1) *Dedicated donations.* (i) You must test donations of human blood and blood components from a donor whose donations are dedicated to and used solely by a single identified recipient under paragraphs (a), (b), and (e) of this section; except that, if the donor makes multiple donations for a single identified recipient, you may perform such testing only on the first donation in each 30-day period. If an untested dedicated donation is made available for any use other than transfusion to the single, identified recipient, then this exemption from the testing required under this section no longer applies.

(ii) Each donation must be labeled as required under §606.121 of this chapter and with a label entitled "INTENDED RECIPIENT INFORMATION LABEL" containing the name and identifying information of the recipient. Each donation must also have the following label, as appropriate:

Donor Testing Status	Label
Tests negative	Label as required under §606.121
Tested negative within the last 30 days	"DONOR TESTED WITHIN THE LAST 30 DAYS"

(2) *Source Plasma.* You are not required to test donations of Source Plasma for evidence of infection due to the communicable disease agents listed in paragraphs (a)(5) and (a)(6) of this section.

(3) *Medical device.* (i) You are not required to test donations of human blood or blood components intended solely as a component of, or used to prepare, a medical device for evidence of infection due to the communicable disease agents listed in paragraphs (a)(5) and (a)(6) of this section unless the final device contains viable leukocytes.

(ii) Donations of human blood and blood components intended solely as a component of, or used to prepare, a medical device must be labeled "Caution: For Further Manufacturing Use as a Component of, or to Prepare, a Medical Device."

(4) *Samples.* You are not required to test samples of blood, blood components, plasma, or sera if used or distributed for clinical laboratory testing or research purposes and not intended for administration to humans or in the manufacture of a product.

(d) *Autologous donations.* You, an establishment that collects human blood or blood components from autologous donors, or you, an establishment that

is a consignee of a collecting establishment, are not required to test donations of human blood or blood components from autologous donors for evidence of infection due to communicable disease agents listed in paragraph (a) of this section or by a serological test for syphilis under paragraph (i) of this section, except:

(1) If you allow any autologous donation to be used for allogeneic transfusion, you must assure that all autologous donations are tested under this section.

(2) If you ship autologous donations to another establishment that allows autologous donations to be used for allogeneic transfusion, you must assure that all autologous donations shipped to that establishment are tested under this section.

(3) If you ship autologous donations to another establishment that does not allow autologous donations to be used for allogeneic transfusion, you must assure that, at a minimum, the first donation in each 30-day period is tested under this section.

(4) Each autologous donation must be labeled as required under § 606.121 of this chapter and with the following label, as appropriate:

Donor Testing Status	Label
Untested	"DONOR UNTESTED"
Tests negative	Label as required under § 606.121
Reactive on current collection/reactive in the last 30 days	"BIOHAZARD" legend in § 610.40(h)(2)(ii)(B)
Tested negative within the last 30 days	"DONOR TESTED WITHIN THE LAST 30 DAYS"

(e) *Further testing.* You must further test each donation, including autologous donations, found to be reactive by a screening test performed under paragraphs (a) and (b) of this section, whenever a supplemental (additional, more specific) test has been approved for such use by FDA, except:

(1) For autologous donations, you must further test under this paragraph, at a minimum, the first reactive donation in each 30-day period; or

(2) If you have a record for that donor of a positive result on a supplemental (additional, more specific) test approved for such use by FDA, you do not have to further test an autologous donation.

(f) *Testing responsibility.* Required testing under this section, must be performed by a laboratory registered in accordance with part 607 of this chapter and either certified to perform such testing on human specimens under the Clinical Laboratory Improvement Amendments of 1988 (42 U.S.C. 263a) under 42 CFR part 493 or has met equivalent requirements as determined by the Health Care Financing Administration in accordance with those provisions.

(g) *Release or shipment prior to testing.* Human blood or blood components that are required to be tested for evidence of infection due to communicable disease agents designated in paragraphs (a) and (i) of this section may be released or shipped prior to completion of testing in the following circumstances provided that you label the blood or blood components under § 606.121(h) of this chapter, you complete the tests for evidence of infection due to communicable disease agents as soon as possible after release or shipment, and that you provide the results promptly to the consignee:

(1) Only in appropriately documented medical emergency situations; or

(2) For further manufacturing use as approved in writing by FDA.

(h) *Restrictions on shipment or use*—(1) *Reactive screening test.* You must not ship or use human blood or blood components that have a reactive screening test for evidence of infection due to a communicable disease agent(s) designated in paragraphs (a) and (i) of this section or that are collected from a donor with a previous record of a reactive screening test for evidence of infection due to a communicable disease agent(s) designated in paragraphs (a) and (i) of this section, except as provided in paragraphs (h)(2)(i) through (h)(2)(vii) of this section.

(2) *Exceptions.* (i) You may ship or use blood or blood components intended for autologous use, including reactive donations, as described in paragraph (d) of this section.

(ii) You must not ship or use human blood or blood components that have a reactive screening test for evidence of infection due to a communicable disease agent(s) designated in paragraph (a) of this section or that are collected

from a donor deferred under §610.41(a) unless you meet the following conditions:

(A) Except for autologous donations, you must obtain from FDA written approval for the shipment or use;

(B) You must appropriately label such blood or blood components as required under §606.121 of this chapter, and with the "BIOHAZARD" legend;

(C) Except for autologous donations, you must label such human blood and blood components as reactive for the appropriate screening test for evidence of infection due to the identified communicable disease agent(s);

(D) If the blood or blood components are intended for further manufacturing use into injectable products, you must include a statement on the container label indicating the exempted use specifically approved by FDA.

(E) Each blood or blood component with a reactive screening test and intended solely as a component of, or used to prepare a medical device, must be labeled with the following label, as appropriate:

Type of Medical Device	Label
A medical device other than an in vitro diagnostic reagent	"Caution: For Further Manufacturing Use as a Component of a Medical Device For Which There Are No Alternative Sources"
An in vitro diagnostic reagent	"Caution: For Further Manufacturing Into In Vitro Diagnostic Reagents For Which There Are No Alternative Sources"

(iii) The restrictions on shipment or use do not apply to samples of blood, blood components, plasma, or sera if used or distributed for clinical laboratory testing or research purposes, and not intended for administration in humans or in the manufacture of a product.

(iv) You may use human blood or blood components from a donor with a previous record of a reactive screening test(s) for evidence of infection due to a communicable disease agent(s) designated in paragraph (a) of this section, if:

(A) At the time of donation, the donor is shown or was previously shown to be suitable by a requalification method or process found acceptable for such purposes by FDA under §610.41(b); and

(B) tests performed under paragraphs (a) and (b) of this section are nonreactive.

(v) Anti-HBc reactive donations, otherwise nonreactive when tested as required under this section, may be used for further manufacturing into plasma derivatives without prior FDA approval or a "BIOHAZARD" legend as required under paragraphs (h)(2)(ii)(A) and (h)(2)(ii)(B) of this section.

(vi) You may use human blood or blood components, excluding Source Plasma, that test reactive by a screening test for syphilis as required under paragraph (i) of this section if, consistent with §640.5 of this chapter, the donation is further tested by an adequate and appropriate test which demonstrates that the reactive screening test is a biological false positive. You must label the blood or blood components with both test results.

(vii) You may use Source Plasma from a donor who tests reactive by a screening test for syphilis as required under §610.40(i) of this chapter, if the donor meets the requirements of §640.65(b)(2) of this chapter.

(i) *Syphilis testing.* In addition to the testing otherwise required under this section, you must test by a serological test for syphilis under §§640.5(a), 640.14, 640.23(a), 640.33(a), 640.53(a), and 640.65(b)(1) and (b)(2) of this chapter.

[66 FR 31162, June 11, 2001, as amended at 77 FR 18, Jan. 3, 2012]

§610.41 Donor deferral.

(a) You, an establishment that collects human blood or blood components, must defer donors testing reactive by a screening test for evidence of infection due to a communicable disease agent(s) listed in §610.40(a) or reactive for a serological test for syphilis under §610.40(i), from future donations of human blood and blood components, except:

(1) You are not required to defer a donor who tests reactive for anti-HBc or anti-HTLV, types I or II, on only one occasion. When a supplemental (additional, more specific) test for anti-HBc or anti-HTLV, types I and II, has been approved for use under §610.40(e) by FDA, such a donor must be deferred;

(2) A deferred donor who tests reactive for evidence of infection due to a

communicable disease agent(s) listed in § 610.40(a) may serve as a donor for blood or blood components shipped or used under § 610.40(h)(2)(ii);

(3) A deferred donor who showed evidence of infection due to hepatitis B surface antigen (HBsAg) when previously tested under § 610.40(a), (b), and (e) subsequently may donate Source Plasma for use in the preparation of Hepatitis B Immune Globulin (Human) provided the current donation tests nonreactive for HBsAg and the donor is otherwise determined to be suitable;

(4) A deferred donor, who otherwise is determined to be suitable for donation and tests reactive for anti-HBc or for evidence of infection due to HTLV, types I and II, may serve as a donor of Source Plasma;

(5) A deferred donor who tests reactive for a communicable disease agent(s) described under § 610.40(a) or reactive with a serological test for syphilis under § 610.40(i), may serve as an autologous donor under § 610.40(d).

(b) A deferred donor subsequently may be found to be suitable as a donor of blood or blood components by a requalification method or process found acceptable for such purposes by FDA. Such a donor is considered no longer deferred.

(c) You must comply with the requirements under §§ 610.46 and 610.47 when a donor tests reactive by a screening test for HIV or HCV required under § 610.40(a) and (b), or when you are aware of other reliable test results or information indicating evidence of HIV or HCV infection.

[66 FR 31164, June 11, 2001, as amended at 72 FR 48798, Aug. 24, 2007]

§ 610.42 Restrictions on use for further manufacture of medical devices.

(a) In addition to labeling requirements in subchapter H of this chapter, when a medical device contains human blood or a blood component as a component of the final device, and the human blood or blood component was found to be reactive by a screening test performed under § 610.40(a) and (b) or reactive for syphilis under § 610.40(i), then you must include in the device labeling a statement of warning indicating that the product was manufactured from a donation found to be reactive by a screening test for evidence of infection due to the identified communicable disease agent(s).

(b) FDA may approve an exception or alternative to the statement of warning required in paragraph (a) of this section based on evidence that the reactivity of the human blood or blood component in the medical device presents no significant health risk through use of the medical device.

[66 FR 31164, June 11, 2001]

§ 610.44 Use of reference panels by manufacturers of test kits.

(a) When available and appropriate to verify acceptable sensitivity and specificity, you, a manufacturer of test kits, must use a reference panel you obtain from FDA or from an FDA designated source to test lots of the following products. You must test each lot of the following products, unless FDA informs you that less frequent testing is appropriate, based on your consistent prior production of products of acceptable sensitivity and specificity:

(1) A test kit approved for use in testing donations of human blood and blood components for evidence of infection due to communicable disease agents listed in § 610.40(a); and

(2) Human immunodeficiency virus (HIV) test kit approved for use in the diagnosis, prognosis, or monitoring of this communicable disease agent.

(b) You must not distribute a lot that is found to be not acceptable for sensitivity and specificity under § 610.44(a). FDA may approve an exception or alternative to this requirement. Applicants must submit such requests in writing. However, in limited circumstances, such requests may be made orally and permission may be given orally by FDA. Oral requests and approvals must be promptly followed by written requests and written approvals.

[66 FR 31164, June 11, 2001]

§ 610.46 Human immunodeficiency virus (HIV) "lookback" requirements.

(a) If you are an establishment that collects Whole Blood or blood components, including Source Plasma and

Source Leukocytes, you must establish, maintain, and follow an appropriate system for the following actions:

(1) Within 3 calendar days after a donor tests reactive for evidence of human immunodeficiency virus (HIV) infection when tested under §610.40(a) and (b) or when you are made aware of other reliable test results or information indicating evidence of HIV infection, you must review all records required under §606.160(d) of this chapter, to identify blood and blood components previously donated by such a donor. For those identified blood and blood components collected:

(i) Twelve months and less before the donor's most recent nonreactive screening tests, or

(ii) Twelve months and less before the donor's reactive direct viral detection test, e.g., nucleic acid test or HIV p24 antigen test, and nonreactive antibody screening test, whichever is the lesser period, you must:

(A) Quarantine all previously collected in-date blood and blood components identified under paragraph (a)(1) of this section if intended for use in another person or for further manufacture into injectable products, except pooled blood components intended solely for further manufacturing into products that are manufactured using validated viral clearance procedures; and

(B) Notify consignees to quarantine all previously collected in-date blood and blood components identified under paragraph (a)(1) of this section if intended for use in another person or for further manufacture into injectable products, except pooled blood components intended solely for further manufacturing into products that are manufactured using validated viral clearance procedures;

(2) You must perform a supplemental (additional, more specific) test for HIV as required under §610.40(e) of this chapter on the reactive donation.

(3) You must notify consignees of the supplemental (additional, more specific) test results for HIV, or the results of the reactive screening test if there is no available supplemental test that is approved for such use by FDA, or if under an investigational new drug application (IND) or investigational device exemption (IDE), is exempted for such use by FDA, within 45 calendar days after the donor tests reactive for evidence of HIV infection under §610.40(a) and (b) of this chapter. Notification of consignees must include the test results for blood and blood components identified under paragraph (a)(1) of this section that were previously collected from donors who later test reactive for evidence of HIV infection.

(4) You must release from quarantine, destroy, or relabel quarantined in-date blood and blood components, consistent with the results of the supplemental (additional, more specific) test performed under paragraph (a)(2) of this section or the results of the reactive screening test if there is no available supplemental test that is approved for such use by FDA, or if under an IND or IDE, exempted for such use by FDA.

(b) If you are a consignee of Whole Blood or blood components, including Source Plasma and Source Leukocytes, you must establish, maintain, and follow an appropriate system for the following actions:

(1) You must quarantine all previously collected in-date blood and blood components identified under paragraph (a)(1) of this section, except pooled blood components intended solely for further manufacturing into products that are manufactured using validated viral clearance procedures, when notified by the collecting establishment.

(2) You must release from quarantine, destroy, or relabel quarantined in-date blood and blood components consistent with the results of the supplemental (additional, more specific) test performed under paragraph (a)(2) of this section, or the results of the reactive screening test if there is no available supplemental test that is approved for such use by FDA, or if under an IND or IDE, is exempted for such use by FDA.

(3) When the supplemental (additional, more specific) test for HIV is positive or when the screening test is reactive and there is no available supplemental test that is approved for such use by FDA, or if under an IND or IDE is exempted for such use by FDA, you must notify transfusion recipients of previous collections of blood and

blood components at increased risk of transmitting HIV infection, or the recipient's physician of record, of the need for recipient HIV testing and counseling. You must notify the recipient's physician of record or a legal representative or relative if the recipient is a minor, deceased, adjudged incompetent by a State court, or, if the recipient is competent but State law permits a legal representative or relative to receive information on behalf of the recipient. You must make reasonable attempts to perform the notification within 12 weeks after receiving the supplemental (additional, more specific) test results for evidence of HIV infection from the collecting establishment, or after receiving the donor's reactive screening test result for HIV if there is no available supplemental test that is approved for such use by FDA, or if under an IND or IDE is exempted for such use by FDA.

(c) Actions under this section do not constitute a recall as defined in § 7.3 of this chapter.

[72 FR 48799, Aug. 24, 2007]

§ 610.47 Hepatitis C virus (HCV) "lookback" requirements.

(a) If you are an establishment that collects Whole Blood or blood components, including Source Plasma and Source Leukocytes, you must establish, maintain, and follow an appropriate system for the following actions:

(1) Within 3 calendar days after a donor tests reactive for evidence of hepatitis C virus (HCV) infection when tested under § 610.40(a) and (b) of this chapter or when you are made aware of other reliable test results or information indicating evidence of HCV infection, you must review all records required under § 606.160(d) of this chapter, to identify blood and blood components previously donated by such a donor. For those identified blood and blood components collected:

(i) Twelve months and less before the donor's most recent nonreactive screening tests, or

(ii) Twelve months and less before the donor's reactive direct viral detection test, e.g., nucleic acid test and nonreactive antibody screening test, whichever is the lesser period, you must:

(A) Quarantine all previously collected in-date blood and blood components identified under paragraph (a)(1) of this section if intended for use in another person or for further manufacture into injectable products, except pooled blood components intended solely for further manufacturing into products that are manufactured using validated viral clearance procedures; and

(B) Notify consignees to quarantine all previously collected in-date blood and blood components identified under paragraph (a)(1) of this section if intended for use in another person or for further manufacture into injectable products, except pooled blood components intended solely for further manufacturing into products that are manufactured using validated viral clearance procedures;

(2) You must perform a supplemental (additional, more specific) test for HCV as required under § 610.40(e) on the reactive donation.

(3) You must notify consignees of the supplemental (additional, more specific) test results for HCV, or the results of the reactive screening test if there is no available supplemental test that is approved for such use by FDA, or if under an investigational new drug application (IND) or investigational device exemption (IDE), is exempted for such use by FDA, within 45 calendar days after the donor tests reactive for evidence of HCV infection under § 610.40(a) and (b). Notification of consignees must include the test results for blood and blood components identified under paragraph (a)(1) of this section that were previously collected from donors who later test reactive for evidence of HCV infection.

(4) You must release from quarantine, destroy, or relabel quarantined in-date blood and blood components consistent with the results of the supplemental (additional, more specific) test performed under paragraph (a)(2) of this section, or the results of the reactive screening test if there is no available supplemental test that is approved for such use by FDA, or if under an IND or IDE, exempted for such use by FDA.

(b) If you are a consignee of Whole Blood or blood components, including Source Plasma or Source Leukocytes,

you must establish, maintain, and follow an appropriate system for the following actions:

(1) You must quarantine all previously collected in-date blood and blood components identified under paragraph (a)(1) of this section, except pooled blood components intended solely for further manufacturing into products that are manufactured using validated viral clearance procedures, when notified by the collecting establishment.

(2) You must release from quarantine, destroy, or relabel quarantined in-date blood and blood components, consistent with the results of the supplemental (additional, more specific) test performed under paragraph (a)(2) of this section, or the results of the reactive screening test if there is no available supplemental test that is approved for such use by FDA, or if under an IND or IDE, is exempted for such use by FDA.

(3) When the supplemental (additional, more specific) test for HCV is positive or when the screening test is reactive and there is no available supplemental test that is approved for such use by FDA, or if under an IND or IDE, is exempted for such use by FDA, you must notify transfusion recipients of previous collections of blood and blood components at increased risk of transmitting HCV infection, or the recipient's physician of record, of the need for recipient HCV testing and counseling. You must notify the recipient's physician of record or a legal representative or relative if the recipient is a minor, adjudged incompetent by a State court, or if the recipient is competent but State law permits a legal representative or relative to receive information on behalf of the recipient. You must make reasonable attempts to perform the notification within 12 weeks after receiving the supplemental (additional, more specific) test results for evidence of HCV infection from the collecting establishment, or after receiving the donor's reactive screening test result for HCV if there is no available supplemental test that is approved for such use by FDA, or if under an IND or IDE, is exempted for such use by FDA.

(c) Actions under this section do not constitute a recall as defined in §7.3 of this chapter.

[72 FR 48799, Aug. 24, 2007]

§610.48 Hepatitis C virus (HCV) "lookback" requirements based on review of historical testing records.

(a) Establishments that collect Whole Blood or blood components, including Source Plasma and Source Leukocytes, must complete the following actions by February 19, 2009.

(b) If you are an establishment that collects Whole Blood or blood components, including Source Plasma and Source Leukocytes, you must establish, maintain, and follow an appropriate system for the following actions:

(1) You must:

(i) Review all records of donor testing for hepatitis C virus (HCV) performed before February 20, 2008. The review must include records dating back indefinitely for computerized electronic records, and to January 1, 1988, for all other records. Record review, quarantine, testing, notification, and disposition performed before February 20, 2008 that otherwise satisfy the requirements under §610.47, are exempt from this section.

(ii) Identify donors who tested reactive for evidence of HCV infection. Donors who tested reactive by a screening test and negative by an appropriate supplemental (additional, more specific) test under §610.40(e) for evidence of HCV infection on the same donation are not subject to further action.

(iii) Identify the blood and blood components previously collected from such donors:

(A) Twelve months and less before the donor's most recent nonreactive screening tests, or

(B) Twelve months and less before the donor's reactive direct viral detection test, e.g., nucleic acid test and nonreactive antibody screening test, whichever is the lesser period.

(2) If you did not perform a supplemental (additional, more specific) test at the time of the reactive donation, you may perform a supplemental test or a licensed screening test with known greater sensitivity than the test of record using either a frozen sample from the same reactive donation or a

fresh sample from the same donor, if obtainable. If neither is available, proceed with paragraphs (b)(3), (b)(4), and (b)(5) of this section.

(3) You must, within 3 calendar days after identifying the blood and blood components previously collected from donors who tested reactive for evidence of HCV infection:

(i) Quarantine all previously collected in-date blood and blood components identified under paragraph (b)(1)(iii) of this section if intended for use in another person or for further manufacture into injectable products, except pooled components solely intended for further manufacturing into products that are manufactured using validated viral clearance procedures.

(ii) Notify consignees to quarantine all previously collected in-date blood and blood components identified under paragraph (b)(1)(iii) of this section if intended for use in another person or for further manufacture into injectable products, except pooled blood components intended solely for further manufacturing into products that are manufactured using validated viral clearance procedures; and

(iii) Notify consignees of the donor's test results, including the results of a supplemental (additional, more specific) test or a licensed screening test with known greater sensitivity than the test of record, if available at that time.

(4) You must notify consignees of the results of the supplemental (additional, more specific) test or the licensed screening test with known greater sensitivity than the test of record for HCV, if performed, within 45 calendar days of completing the further testing. Notification of consignees must include the test results for blood and blood components identified under paragraph (b)(1)(iii) of this section that were previously collected from a donor who later tests reactive for evidence of HCV infection.

(5) You must release from quarantine, destroy, or relabel quarantined in-date blood and blood components consistent with the results of the further testing performed under paragraph (b)(2) of this section or the results of the reactive screening test if there is no available supplemental test that is approved for such use by FDA, or if under an investigational new drug application (IND) or investigational device exemption (IDE), is exempted for such use by FDA.

(c) If you are a consignee of Whole Blood or blood components, including Source Plasma and Source Leukocytes, you must establish, maintain, and follow an appropriate system for the following actions, which you must complete within 1 year of the date of notification by the collecting establishment:

(1) You must quarantine all previously collected in-date blood and blood components identified under paragraph (b)(1)(iii) of this section, except pooled blood components solely intended for further manufacturing into products that are manufactured using validated viral clearance procedures, when notified by the collecting establishment.

(2) You must release from quarantine, destroy, or relabel quarantined in-date blood and blood components, consistent with the results of the further testing performed under paragraph (b)(2) of this section, or the results of the reactive screening test if there is no available supplemental test that is approved for such use by FDA, or if under an IND or IDE is exempted for such use by FDA.

(3) When the supplemental (additional, more specific) test for HCV is positive; or the supplemental test is indeterminate, but the supplemental test is known to be less sensitive than the screening test; or the screening test is reactive and there is no available supplemental test that is approved for such use by FDA, or if under an IND or IDE, is exempted for such use by FDA; or if supplemental testing is not performed, you must make reasonable attempts to notify transfusion recipients of previous collections of blood and blood components at increased risk of transmitting HCV infection, or the recipient's physician of record, of the need for recipient HCV testing and counseling. You must notify the recipient's physician of record or a legal representative or relative if the recipient is a minor, adjudged incompetent by a State court, or if the recipient is competent but State law permits a legal

representative or relative to receive information on behalf of the recipient.

(d) Actions under this section do not constitute a recall as defined in § 7.3 of this chapter.

(e) This section will expire on August 24, 2015.

[72 FR 48800, Aug. 24, 2007]

Subpart F—Dating Period Limitations

§ 610.50 Date of manufacture.

The date of manufacture shall be determined as follows:

(a) For products for which an official standard of potency is prescribed in either § 610.20 or § 610.21, or which are subject to official potency tests, the date of initiation by the manufacturer of the last valid potency test.

(b) For products that are not subject to official potency tests, (1) the date of removal from animals, (2) the date of extraction, (3) the date of solution, (4) the date of cessation of growth, or (5) the date of final sterile filtration of a bulk solution, whichever is applicable.

[38 FR 32056, Nov. 20, 1973, as amended at 42 FR 27582, May 31, 1977]

§ 610.53 Dating periods for licensed biological products.

(a) *General.* The minimum dating periods in paragraph (c) of this section are based on data relating to usage, clinical experience, or laboratory tests that establish the reasonable period beyond which the product cannot be expected to yield its specific results and retain its safety, purity, and potency, provided the product is maintained at the recommended temperatures. The standards prescribed by the regulations in this subchapter are designed to ensure the continued safety, purity, and potency of the products and are based on the dating periods set forth in paragraph (c) of this section. Package labels for each product shall recommend storage at the stated temperatures.

(b) *When the dating period begins.* The dating period for a product shall begin on the date of manufacture, as prescribed in § 610.50. The dating period for a combination of two or more products shall be no longer than the dating period of the component with the shortest dating period.

(c) *Table of dating periods.* In using the table in this paragraph, a product in column A may be stored by the manufacturer at the prescribed temperature and length of time in either column B or C, plus the length of time in column D. The dating period in column D shall be applied from the day the product leaves the manufacturer's storage, provided the product has not exceeded its maximum storage period, as prescribed in column B or C. If a product is held in the manufacturer's storage beyond the period prescribed, the dating period for the product being distributed shall be reduced by a corresponding period.

A	B	C	D
Product	Manufacturer's storage period 1 to 5 °C (unless otherwise stated)	Manufacturer's storage period 0 °C or colder (unless otherwise stated)	Dating period after leaving manufacturer's storage when stored at 2 to 8 °C (unless otherwise stated)
Adenovirus Vaccine Live Oral	6 months	Not applicable	6 months.
Albumin (Human)	3 years	....do	(a) 5 years.
	....do	....do	(b) 3 years, provided labeling recommends storage at room temperature, no warmer than 37 °C.
	Not applicable	....do	(c) 10 years, if in a hermetically sealed metal container and provided labeling recommends storage between 2 and 8 °C.
Allergenic Extracts labeled "No U.S. Standard of Potency":			
1. With 50 percent or more glycerin.	3 years	....do	3 years.
2. With less than 50 percent glycerin.	18 months	....do	18 months.
3. Products for which cold storage conditions are inappropriate.	Not applicable	....do	18 months (from date of manufacture), provided labeling recommends storage at 30 °C or colder.

A	B	C	D
Product	Manufacturer's storage period 1 to 5 °C (unless otherwise stated)	Manufacturer's storage period 0 °C or colder (unless otherwise stated)	Dating period after leaving manufacturer's storage when stored at 2 to 8 °C (unless otherwise stated)
4. Powders and tablets	....do	....do	5 years (from date of manufacture), provided labeling recommends storage at 30 °C or colder.
5. Freeze-dried products:			
a. Unreconstituted	....do	....do	4 years (from date of manufacture).
b. Reconstituted	....do	....do	18 months (cannot exceed 4-year unreconstituted dating period plus an additional 12 months).
Allergenic Extracts, Alum Precipitated labeled "No U.S. Standard of Potency".	18 months	....do	18 months.
Anthrax Vaccine Adsorbed	2 years	....do	1 year.
Antibody to Hepatitis B Surface Antigen:			
1. Antibody to Hepatitis B Surface Antigen.	6 months	....do	6 months.
2. Lyophilized coated red blood cells.	....do	....do	Do.
3. Enzyme conjugated products	....do	....do	Do.
Iodinated (^{125}I) products	Not applicable	....do	45 days (from date of manufacture).
Antihemophilic Factor (Human)	....do	....do	1 year (from date of manufacture).
Anti-Human Globulin Liquid	....do	....do	2 years.
Anti-Inhibitor Coagulant Complex	....do	....do	Do.
Antirabies Serum	1 year	....do	Do.
Antivenin (*Crotalidae*) Polyvalent	....do	....do	5 years with an initial 10 percent excess of potency, provided labeling recommends storage at 37 °C or colder.
Antivenin (*Latrodectus Mactans*)	....do	....do	5 years with an initial 10 percent excess of potency.
Antivenin (*Micurus fulvius*)	....do	....do	Do.
Asparaginase	Not applicable	....do	18 months from the date of the last valid potency test.
BCG Vaccine	1 year	Not applicable	6 months.
Blood Grouping Reagents			
1. Liquid	Not applicable	Not applicable	2 years.
2. Dried	1 year	2 years	5 years.
Blood Group Substance AB	....do	....do	2 years.
Blood Group Substance A	....do	....do	Do.
Blood Group Substance B	....do	....do	Do.
Botulism Antitoxin	....do	Not applicable	5 years with an initial 20 percent excess of potency.
Cholera Vaccine	....do	....do	18 months.
Coccidioidin	....do	....do	3 years.
Collagenase	Not applicable	....do	4 years (from date of manufacture), provided labeling recommends storage at 37 °C or colder.
Cryoprecipitated AHF	....do	....do	12 months from the date of collection of source blood, provided labeling recommends storage at −18 °C or colder.
Diphtheria Antitoxin:			
1. Liquid	1 year	....do	5 years with an initial 20 percent excess of potency.
2. Dried	....do	2 years	5 years with an initial 10 percent excess of potency.
Diphtheria and Tetanus Toxoids and Pertussis Vaccine Adsorbed.	....do	Not applicable	18 months.
Diphtheria and Tetanus Toxoids, Adsorbed.	....do	....do	2 years.
Diphtheria Toxin for Schick Test	....do	....do	1 year.
Diphtheria Toxoid	....do	....do	2 years.
Diphtheria Toxoid Adsorbed	....do	2 years	Do.
Diphtheria Toxoid-Schick Test Control	Not applicable	Not applicable	1 year.
Factor IX Complex	....do	....do	1 year (from date of manufacture).
Fibrinolysin (Human)	1 year	2 years	2 years.
Fibrinolysin and Desoxyribonuclease Combined (Bovine).	....do	....do	3 years, provided labeling recommends storage at 30 °C or colder.
Fibrinolysin and Desoxyribonuclease Combined (Bovine) with Chloramphenicol.	....do	....do	Do.
Hepatitis B Surface Antigen:			
1. Unlyophilized coated red blood cells.	Not applicable	....do	14 days (from date of manufacture).

A	B	C	D
Product	Manufacturer's storage period 1 to 5 °C (unless otherwise stated)	Manufacturer's storage period 0 °C or colder (unless otherwise stated)	Dating period after leaving manufacturer's storage when stored at 2 to 8 °C (unless otherwise stated)
2. Iodinated (^{125}I) product	....do	....do	45 days (from date of manufacture).
3. Enzyme conjugated product	6 months	....do	6 months.
Histoplasmin	1 year	Not applicable	2 years.
Immunoglobulins:			
1. Hepatitis B Immune Globulin (Human).	Not applicable	....do	1 year.
2. Immune Globulin (Human)	3 years	....do	3 years.
3. Immune Globulin Intravenous (Human).	Not applicable	....do	1 year.
4. Lymphocyte Immune Globulin, Anti-Thymocyte Globulin (Equine).	....do	Not applicable	2 years.
5. Pertussis Immune Globulin (Human).	3 years	....do	3 years from date the dried or frozen bulk product is placed in final solution.
6. Rabies Immune Globulin (Human).	1 year	....do	1 year.
7. Rh_o(D) Immune Globulin (Human).	6 months	....do	6 months.
8. Tetanus Immune Globulin (Human).	1 year	....do	3 years with an initial 10 percent excess of potency.
9. Vaccinia Immune Globulin (Human).	3 years	....do	3 years.
10. Varicella-Zoster Immune Globulin (Human).	Not applicable	....do	1 year.
Hepatitis B Vaccine	2 years at 2 to 8 °C.	Not applicable	3 years.
Influenza Virus Vaccine	1 year	....do	18 months.
Limulus Amebocyte Lysate	Not applicable	Not applicable	18 months (from date of manufacture).
Measles, Mumps, and Rubella Virus Vaccine Live.	....do	1 year (−20 °C or colder).	1 year.
Measles and Mumps Virus Vaccine Live	....do	....do	1 year.
Measles and Rubella Virus Vaccine Live	....do	....do	Do.
Measles Live and Smallpox Vaccine	Not applicable	....do	1 year (from date of manufacture).
Measles Virus Vaccine Live	....do	....do	1 year.
Meningococcal Polysaccharide Vaccine Group A:			
1. Final bulk powder	....do	2 years (−20 °C or colder).	Not applicable.
2. Final container	Not applicable	3 years (−20 °C or colder).	2 years.
Meningococcal Polysaccharide Vaccine Group C:			
1. Final bulk powder	....do	2 years (−20 °C or colder).	Not applicable.
2. Final container	....do	3 years (−20 °C or colder).	2 years.
Meningococcal Polysaccharide Vaccine Groups A and C combined:			
1. Final bulk powder	....do	2 years (−20 °C or colder).	Not applicable.
2. Final container	....do	3 years (−20 °C or colder).	2 years.
Meningococcal Polysaccharide Vaccine Groups A, C, Y, and W135 combined:			
1. Final bulk power	....do	2 years (−20 °C or colder).	Not applicable.
2. Final container	....do	3 years (−20 °C or colder).	2 years.
Mumps Skin Test Antigen	6 months	Not applicable	18 months.
Mumps Virus Vaccine Live	Not applicable	1 year (−20 °C or colder).	1 year.
Normal Horse Serum	1 year	2 years	5 years.
Pertussis Vaccine	....do	Not applicable	18 months.
Pertussis Vaccine Adsorbed	....do	....do	Do.
Plague Vaccine	....do	....do	Do.
Plasma products:			
1. Fresh Frozen Plasma	Not applicable	....do	1 year from date of collection of source blood (−18 °C or colder).

A	B	C	D
Product	Manufacturer's storage period 1 to 5 °C (unless otherwise stated)	Manufacturer's storage period 0 °C or colder (unless otherwise stated)	Dating period after leaving manufacturer's storage when stored at 2 to 8 °C (unless otherwise stated)
2. Liquid Plasma	....do	....do	(a) 26 days from date of collection of source blood (between 1 and 6 °C). (b) 40 days from date of collection of source blood only when CPDA–1 solution is used as the anticoagulant (between 1 and 6 °C).
3. Plasma	....do	....do	5 years from date of collection of source blood (–18 °C or colder).
4. Platelet Rich Plasma	....do	....do	72 hours from time of collection of source blood, provided labeling recommends storage (20 to 24 °C or between 1 and 6 °C). 5 days if certain approved containers are used (20 to 24 °C).
5. Source Leukocytes	....do	....do	In lieu of expiration date, the collection date shall appear on the label.
6. Source Plasma	....do	....do	10 years (at the recommended storage temperature stated on the label).
7. Therapeutic Exchange Plasma	....do	....do	10 years.
Plasma Protein Fraction (Human)	1 year	....do	(a) 5 years. (b) 3 years provided labeling recommends storage at room temperature, no warmer than 30 °C).
Platelets	Not applicable	....do	72 hours from time of collection of source blood, provided labeling recommends storage at 20 to 24 °C or between 1 and 6 °C, or as specified in the directions for use for the blood collecting, processing, and storage system approved for such use by the Director, Center for Biologics Evaluation and Research (CBER).
Pneumococcal Vaccine Polyvalent:			
1. Final bulk powder	....do	24 months after potency assay (–20 °C or colder).	Not applicable.
2. Final container	....do	Not applicable	2 years (from date of manufacture).
Poliovirus Vaccine Inactivated	1 year	....do	1 year.
Poliovirus Vaccine Live Oral Trivalent:			
1. Frozen	Not applicable	1 year (–10 °C or colder).	1 year, provided labeling recommends storage at a temperature which will maintain ice continuously in a solid state.
2. Liquid	....do	Not applicable	30 days, provided labeling recommends storage between 2 and 8 °C and container has been unopened.
Poliovirus Vaccine Live Oral Type I:			
1. Frozen	....do	1 year (–10 °C or colder).	1 year, provided labeling recommends storage at a temperature which will maintain ice continuously in a solid state.
2. Liquid	....do	Not applicable	30 days, provided labeling recommends storage between 2 and 8 °C and container has been unopened.
Poliovirus Vaccine Live Oral Type II:			
1. Frozen	....do	1 year (–10 °C or colder).	1 year, provided labeling recommends storage at a temperature which will maintain ice continuously in a solid state.
2. Liquid	....do	Not applicable	30 days, provided labeling recommends storage between 2 and 8 °C and container has been unopened.
Poliovirus Vaccine Live Oral Type III:			
1. Frozen	....do	1 year (–10 °C or colder).	1 year, provided labeling recommends storage at a temperature which will maintain ice continuously in a solid state.

A	B	C	D
Product	Manufacturer's storage period 1 to 5 °C (unless otherwise stated)	Manufacturer's storage period 0 °C or colder (unless otherwise stated)	Dating period after leaving manufacturer's storage when stored at 2 to 8 °C (unless otherwise stated)
2. Liquid	....do	Not applicable	30 days, provided labeling recommends storage between 2 and 8 °C and container has been unopened.
Polyvalent bacterial antigens with "No U.S. Standard of Potency" liquid.	1 year	....do	18 months.
Polyvalent bacterial vaccines with "No U.S. Standard of Potency" liquid.	....do	....do	Do.
Rabies Vaccine:			
1. Dried	....do	2 years	Do.
2. Liquid	3 months	Not applicable	6 months.
Reagent red blood cells	Not applicable	Not applicable	Thirty-five days from earliest date of collection if kept in liquid form (indefinite storage of reagent red blood cell source material at −65 °C or colder).
ACD Red Blood Cells	....do	....do	(a) 21 days from date of collection of source blood, provided labeling recommends storage between 1 and 6 °C and the hermetic seal is not broken during processing. (b) 24 hours after plasma removal, provided labeling recommends storage between 1 and 6 °C and the hermetic seal is broken during processing.
CPD Red Blood Cells	....do	....do	(a) 21 days from date of collection of source blood, provided labeling recommends storage between 1 and 6 °C and the hermetic seal is not broken during processing. (b) 24 hours after plasma removal, provided labeling recommends storage between 1 and 6 °C and the hermetic seal is broken during processing.
CPDA–1 Red Blood Cells	....do	....do	(a) 35 days from date of collection of source blood, provided labeling recommends storage between 1 and 6 °C and the hermetic seal is not broken during processing. (b) 24 hours after plasma removal, provided labeling recommends storage between 1 and 6 °C and the hermetic seal is broken during processing.
Red Blood Cells Deglycerolized	....do	....do	24 hours after removal from storage at −65 °C or colder, provided labeling recommends storage between 1 and 6 °C, or as specified in the directions for use for the blood collecting, processing, and storage system approved for such use by the Director, CBER.
Red Blood Cells Frozen	....do	....do	10 years from date of collection of source blood, provided labeling recommends storage at −65 °C or colder, or as specified in the directions for use for the blood collecting, processing, and storage system approved for such use by the Director, CBER.
Rubella and Mumps Virus Vaccine Live	....do	1 year (−20 °C or colder).	1 year.
Rubella Virus Vaccine Live	....do	....do	Do.
Skin Test Antigens for Cellular Hypersensitivity.	6 months	Not applicable	Do.

A	B	C	D
Product	Manufacturer's storage period 1 to 5 °C (unless otherwise stated)	Manufacturer's storage period 0 °C or colder (unless otherwise stated)	Dating period after leaving manufacturer's storage when stored at 2 to 8 °C (unless otherwise stated)
Smallpox Vaccine:			
1. Liquid	Not applicable	9 months (−10 °C or colder, if product is maintained as glycerinated or equivalent vaccine in bulk or final containers).	3 months, provided labeling recommends storage at 0 °C or colder.
2. Dried	6 months	Not applicable	18 months.
Streptokinase	Not applicable	do	Do.
Tetanus and Diphtheria Toxoids Adsorbed for Adult Use.	1 year	do	2 years.
Tetanus Antitoxin:			
1. Liquid	do	do	5 years with an initial 20 percent excess or potency.
2. Dried	do	2 years	5 years with an initial 10 percent excess or potency.
Tetanus Toxoid	do	Not applicable	2 years.
Tetanus Toxoid Adsorbed	do	do	Do.
Thrombin	do	2 year	3 years.
Thrombin Impregnated Pad	Not applicable	Not applicable	1 year, or 6 months at 20 to 24 °C.
Tuberculin:			
1. Purified Protein Derivative, diluted.	6 months	do	1 year.
2. Old or Purified Protein Derivative dried on multiple puncture device.	1 year (not to exceed 30 °C; do not refrigerate).	do	2 years, provided labeling recommends storage at a temperature not to exceed 30 °C. Do not refrigerate.
3. Old on multiple puncture device.	do	do	Do.
Typhoid Vaccine	1 year	do	18 months.
ACD Whole Blood	Not applicable	do	21 days from date of collection, provided labeling recommends storage between 1 and 6 °C.
CPD Whole Blood	do	do	Do.
CPDA–1 Whole Blood	do	do	35 days from date of collection, provided labeling recommends storage between 1 and 6 °C.
Heparin Whole Blood	do	do	48 hours from date of collection, provided labeling recommends storage between 1 and 6 °C.
Yellow Fever Vaccine	do	1 year (−20 °C or colder).	1 year, provided labeling recommends storage at 5 °C or colder.

(d) *Exemptions.* Exemptions or modifications shall be made only upon written approval, in the form of a supplement to the biologics license application, issued by the Director, Center for Biologics Evaluation and Research or the Director of the Center for Drug Evaluation and Research.

[50 FR 4134, Jan. 29, 1985, as amended at 51 FR 15607, Apr. 25, 1986; 51 FR 19750, June 2, 1986; 52 FR 37455, Oct. 7, 1987; 53 FR 12764, Apr. 19, 1988; 62 FR 15110, Mar. 31, 1997; 64 FR 56453, Oct. 20, 1999; 70 FR 14985, Mar. 24, 2005; 72 FR 45887, Aug. 16, 2007; 72 FR 54208, Sept. 24, 2007; 73 FR 49942, Aug. 25, 2008]

Subpart G—Labeling Standards

§ 610.60 Container label.

(a) *Full label.* The following items shall appear on the label affixed to each container of a product capable of bearing a full label:

(1) The proper name of the product;

(2) The name, address, and license number of manufacturer;

(3) The lot number or other lot identification;

(4) The expiration date;

(5) The recommended individual dose, for multiple dose containers.

(6) The statement: "'Rx only'" for prescription biologicals.

(7) If a Medication Guide is required under part 208 of this chapter, the statement required under § 208.24(d) of this chapter instructing the authorized dispenser to provide a Medication Guide to each patient to whom the drug is dispensed and stating how the Medication Guide is provided, except where the container label is too small, the required statement may be placed on the package label.

(b) *Package label information.* If the container is not enclosed in a package, all the items required for a package label shall appear on the container label.

(c) *Partial label.* If the container is capable of bearing only a partial label, the container shall show as a minimum the name (expressed either as the proper or common name), the lot number or other lot identification and the name of the manufacturer; in addition, for multiple dose containers, the recommended individual dose. Containers bearing partial labels shall be placed in a package which bears all the items required for a package label.

(d) *No container label.* If the container is incapable of bearing any label, the items required for a container label may be omitted, provided the container is placed in a package which bears all the items required for a package label.

(e) *Visual inspection.* When the label has been affixed to the container a sufficient area of the container shall remain uncovered for its full length or circumference to permit inspection of the contents.

[38 FR 32056, Nov. 20, 1973, as amended at 47 FR 22518, May 25, 1982; 63 FR 66400, Dec. 1, 1998; 67 FR 4907, Feb. 1, 2002]

§ 610.61 Package label.

The following items shall appear on the label affixed to each package containing a product:

(a) The proper name of the product;

(b) The name, address, and license number of manufacturer;

(c) The lot number or other lot identification;

(d) The expiration date;

(e) The preservative used and its concentration, or if no preservative is used and the absence of a preservative is a safety factor, the words "no preservative";

(f) The number of containers, if more than one;

(g) The amount of product in the container expressed as (1) the number of doses, (2) volume, (3) units of potency, (4) weight, (5) equivalent volume (for dried product to be reconstituted), or (6) such combination of the foregoing as needed for an accurate description of the contents, whichever is applicable;

(h) The recommended storage temperature;

(i) The words "Shake Well", "Do not Freeze" or the equivalent, as well as other instructions, when indicated by the character of the product;

(j) The recommended individual dose if the enclosed container(s) is a multiple-dose container;

(k) The route of administration recommended, or reference to such directions in an enclosed circular;

(l) Known sensitizing substances, or reference to an enclosed circular containing appropriate information;

(m) The type and calculated amount of antibiotics added during manufacture;

(n) The inactive ingredients when a safety factor, or reference to an enclosed circular containing appropriate information;

(o) The adjuvant, if present;

(p) The source of the product when a factor in safe administration;

(q) The identity of each microorganism used in manufacture, and, where applicable, the production medium and the method of inactivation, or reference to an enclosed circular containing appropriate information;

(r) Minimum potency of product expressed in terms of official standard of potency or, if potency is a factor and no U.S. standard of potency has been prescribed, the words "No U.S. standard of potency."

(s) The statement: "'Rx only'" for prescription biologicals.

[38 FR 32056, Nov. 20, 1973, as amended at 47 FR 22518, May 25, 1982; 55 FR 10423, Mar. 21, 1990; 67 FR 4907, Feb. 1, 2002]

§ 610.62 Proper name; package label; legible type.

(a) *Position.* The proper name of the product on the package label shall be placed above any trademark or trade

name identifying the product and symmetrically arranged with respect to other printing on the label.

(b) *Prominence.* The point size and typeface of the proper name shall be at least as prominent as the point size and typeface used in designating the trademark and trade name. The contrast in color value between the proper name and the background shall be at least as great as the color value between the trademark and trade name and the background. Typography, layout, contrast, and other printing features shall not be used in a manner that will affect adversely the prominence of the proper name.

(c) *Legible type.* All items required to be on the container label and package label shall be in legible type. "Legible type" is type of a size and character which can be read with ease when held in a good light and with normal vision.

§ 610.63 Divided manufacturing responsibility to be shown.

If two or more licensed manufacturers participate in the manufacture of a biological product, the name, address, and license number of each must appear on the package label, and on the label of the container if capable of bearing a full label.

[64 FR 56453, Oct. 20, 1999]

§ 610.64 Name and address of distributor.

The name and address of the distributor of a product may appear on the label provided that the name, address, and license number of the manufacturer also appears on the label and the name of the distributor is qualified by one of the following phrases: "Manufactured for _____", "Distributed by _____", "Manufactured by _____ for _____", "Manufactured for _____ by _____", "Distributor: _____", or "Marketed by _____". The qualifying phrases may be abbreviated.

[61 FR 57330, Nov. 6, 1996]

§ 610.65 Products for export.

Labels on packages or containers of products for export may be adapted to meet specific requirements of the regulations of the country to which the product is to be exported provided that in all such cases the minimum label requirements prescribed in § 610.60 are observed.

§ 610.67 Bar code label requirements.

Biological products must comply with the bar code requirements at § 201.25 of this chapter. However, the bar code requirements do not apply to devices regulated by the Center for Biologics Evaluation and Research or to blood and blood components intended for transfusion. For blood and blood components intended for transfusion, the requirements at § 606.121(c)(13) of this chapter apply instead.

[69 FR 9171, Feb. 26, 2004]

§ 610.68 Exceptions or alternatives to labeling requirements for biological products held by the Strategic National Stockpile.

(a) The appropriate FDA Center Director may grant an exception or alternative to any provision listed in paragraph (f) of this section and not explicitly required by statute, for specified lots, batches, or other units of a biological product, if the Center Director determines that compliance with such labeling requirement could adversely affect the safety, effectiveness, or availability of such product that is or will be included in the Strategic National Stockpile.

(b)(1)(i) A Strategic National Stockpile official or any entity that manufactures (including labeling, packing, relabeling, or repackaging), distributes, or stores a biological product that is or will be included in the Strategic National Stockpile may submit, with written concurrence from a Strategic National Stockpile official, a written request for an exception or alternative described in paragraph (a) of this section to the Center Director.

(ii) The Center Director may grant an exception or alternative described in paragraph (a) of this section on his or her own initiative.

(2) A written request for an exception or alternative described in paragraph (a) of this section must:

(i) Identify the specified lots, batches, or other units of the biological

product that would be subject to the exception or alternative;

(ii) Identify the labeling provision(s) listed in paragraph (f) of this section that are the subject of the exception or alternative request;

(iii) Explain why compliance with such labeling provision(s) could adversely affect the safety, effectiveness, or availability of the specified lots, batches, or other units of the biological product that are or will be included in the Strategic National Stockpile;

(iv) Describe any proposed safeguards or conditions that will be implemented so that the labeling of the product includes appropriate information necessary for the safe and effective use of the product, given the anticipated circumstances of use of the product;

(v) Provide a draft of the proposed labeling of the specified lots, batches, or other units of the biological product subject to the exception or alternative; and

(vi) Provide any other information requested by the Center Director in support of the request.

(c) The Center Director must respond in writing to all requests under this section.

(d) A grant of an exception or alternative under this section will include any safeguards or conditions deemed appropriate by the Center Director so that the labeling of product subject to the exception or alternative includes the information necessary for the safe and effective use of the product, given the anticipated circumstances of use.

(e) If you are a sponsor receiving a grant of a request for an exception or alternative to the labeling requirements under this section:

(1) You need not submit a supplement under §601.12(f)(1) through (f)(2) of this chapter; however,

(2) You must report any grant of a request for an exception or alternative under this section as part of your annual report under §601.12(f)(3) of this chapter.

(f) The Center Director may grant an exception or alternative under this section to the following provisions of this chapter, to the extent that the requirements in these provisions are not explicitly required by statute:

(1) §610.60;

(2) §610.61(c) and (e) through (r);

(3) §610.62;

(4) §610.63;

(5) §610.64;

(6) §610.65; and

(7) §312.6.

[72 FR 73600, Dec. 28, 2007]

PART 630—GENERAL REQUIREMENTS FOR BLOOD, BLOOD COMPONENTS, AND BLOOD DERIVATIVES

AUTHORITY: 21 U.S.C. 321, 331, 351, 352, 355, 360, 371; 42 U.S.C. 216, 262, 264.

SOURCE: 66 FR 31176, June 11, 2001, unless otherwise noted.

§ 630.6 Donor notification.

(a) *Notification of donors.* You, an establishment that collects blood or blood components, must make reasonable attempts to notify any donor, including an autologous donor, who has been deferred based on the results of tests for evidence of infection with a communicable disease agent(s) as required by §610.41 of this chapter; or who has been determined not to be suitable as a donor based on suitability criteria under §640.3 or §640.63 of this chapter. You must attempt to obtain the results of supplemental testing required under §610.40(e) of this chapter prior to notifying a donor of the deferral. If notification occurs prior to receipt of such results, you must also notify a deferred donor of the results of the supplemental testing. You must notify a donor as described in paragraph (b) of this section.

(b) *Content of notification.* You must provide the following information to a donor deferred or determined not to be suitable as a donor as described in paragraph (a) of this section:

(1) That the donor is deferred or determined not to be suitable for donation and the reason for that decision;

(2) Where appropriate, the types of donation of blood or blood components that the donor should not donate in the future;

(3) Where applicable, the results of tests for evidence of infection due to communicable disease agent(s) that were a basis for deferral under §610.41 of this chapter, including results of

supplemental (i.e., additional, more specific) tests as required in §610.40(e) of this chapter; and,

(4) Where appropriate, information concerning medical followup and counseling.

(c) *Time period for notification.* You must make reasonable attempts to notify the donor within 8 weeks after determining that the donor is deferred or determined not to be suitable for donation as described in paragraph (a) of this section. You must document that you have successfully notified the donor or when you are unsuccessful that you have made reasonable attempts to notify the donor.

(d) *Autologous donors.* (1) You also must provide the following information to the referring physician of an autologous donor who is deferred based on the results of tests for evidence of infection with a communicable disease agent(s) as described in paragraph (a) of this section:

(i) Information that the autologous donor is deferred based on the results of tests for evidence of infection due to communicable disease agent(s), as required under §610.41 of this chapter, and the reason for that decision;

(ii) Where appropriate, the types of donation of blood or blood components that the autologous donor should not donate in the future; and

(iii) The results of tests for evidence of infection due to communicable disease agent(s), that were a basis for deferral under §610.41 of this chapter, including results of supplemental (i.e., additional, more specific) tests as required in §610.40(e) of this chapter.

(2) You must make reasonable attempts to notify the autologous donor's referring physician within 8 weeks after determining that the autologous donor is deferred as described in paragraph (a) of this section. You must document that you have successfully notified the autologous donor's referring physician or when you are unsuccessful that you have made reasonable attempts to notify the physician.

PART 640—ADDITIONAL STANDARDS FOR HUMAN BLOOD AND BLOOD PRODUCTS

Subpart A—Whole Blood

Subpart B—Red Blood Cells

Subpart C—Platelets

Subpart D—Plasma

Subpart E [Reserved]

Subpart F—Cryoprecipitate

Subpart G—Source Plasma

AUTHORITY: 21 U.S.C. 321, 351, 352, 353, 355, 360, 371; 42 U.S.C. 216, 262, 263, 263a, 264.

SOURCE: 38 FR 32089, Nov. 20, 1973, unless otherwise noted.

CROSS REFERENCES: For U.S. Customs Service regulations relating to viruses, serums, and toxins, see 19 CFR 12.21–12.23. For U.S. Postal Service regulations relating to the admissibility to the United States mails see parts 124 and 125 of the Domestic Mail Manual, that is incorporated by reference in 39 CFR part 111.

Subpart A—Whole Blood

§ 640.1 Whole Blood.

The proper name of this product shall be Whole Blood. Whole Blood is defined as blood collected from human donors for transfusion to human recipients.

[38 FR 32089, Nov. 20, 1973, as amended at 50 FR 4138, Jan. 29, 1985]

§ 640.2 General requirements.

(a) *Manufacturing responsibility.* All manufacturing of Whole Blood, including donor examination, blood collection, laboratory tests, labeling, storage and issue, shall be done under the supervision and control of the same licensed establishment except that the Director, Center for Biologics Evaluation and Research, may approve arrangements, upon joint request of two or more licensed establishments, which he finds are of such a nature as to assure compliance otherwise with the provisions of this subchapter.

(b) *Blood container.* The blood container shall not be entered prior to issue for any purpose except for blood collection or when the method of processing requires use of a different container. The container shall be uncolored and transparent to permit visual inspection of the contents and any closure shall be such as will maintain a hermetic seal and prevent contamination of the contents. The container material shall not interact with the contents under the customary conditions of storage and use, in such a manner as to have an adverse effect upon the safety, purity, or potency of the blood.

(c) *Reissue of blood.* Blood that has been removed from storage controlled by a licensed establishment shall not be reissued by a licensed establishment unless the following conditions are observed:

(1) The container has a tamper-proof seal when originally issued and this seal remains unbroken;

(2) A segment is properly attached and has not been removed, except that blood lacking a properly attached segment may be reissued in an emergency provided it is accompanied by instructions for sampling and for use within 6 hours after entering the container for sampling;

(3) The blood has been stored continuously at 1 to 6 °C and shipped between 1 and 10 °C;

(4) The blood is held for observation until a significant inspection consistent with the requirements of § 640.5(e) can be made.

[38 FR 32089, Nov. 20, 1973, as amended at 41 FR 4015, Jan. 28, 1976; 42 FR 59878, Nov. 22, 1977; 43 FR 34460, Aug. 4, 1978; 49 FR 15187, Apr. 18, 1984; 49 FR 23834, June 8, 1984; 50 FR 4138, Jan. 29, 1985; 53 FR 116, Jan. 5, 1988; 55 FR 11013, Mar. 26, 1990; 63 FR 16685, Apr. 6, 1998; 64 FR 45371, Aug. 19, 1999; 66 FR 1836, Jan. 10, 2001; 66 FR 31165, June 11, 2001; 66 FR 40889, Aug. 6, 2001; 67 FR 9587, Mar. 4, 2002]

§ 640.3 Suitability of donor.

(a) *Method of determining.* The suitability of a donor as a source of Whole Blood shall be determined by a qualified physician or by persons under his supervision and trained in determining suitability. Such determination shall be made on the day of collection from the donor by means of medical history, a test for hemoglobin level, and such physical examination as appears necessary to a physician who shall be present on the premises when examinations are made, except that the suitability of donors may be determined when a physician is not present on the premises, provided the establishment (1) maintains on the premises, and files with the Center for Biologics Evaluation and Research, a manual of standard procedures and methods, approved by the Director of the Center for Biologics Evaluation and Research, that shall be followed by employees who determine suitability of donors, and (2) maintains records indicating the name and qualifications of the person immediately in charge of the employees who determine the suitability of donors when a physician is not present on the premises.

(b) *Qualifications of donor; general.* Except as provided in paragraph (f) of this section and for autologous donations, a person may not serve as a source of Whole Blood more than once in 8 weeks. In addition, donors shall be in good health, as indicated in part by:

(1) Normal temperature;

(2) Demonstration that systolic and diastolic blood pressures are within normal limits, unless the examining physician is satisfied that an individual with blood pressures outside these limits is an otherwise qualified donor under the provisions of this section;

(3) For allogeneic donors, a blood hemoglobin level which shall be demonstrated to be no less than 12.5 grams (g) of hemoglobin per 100 milliliters (mL) of blood; or a hematocrit value of 38 percent, and for autologous donors, a blood hemoglobin level which shall be demonstrated to be no less than 11.0 g of hemoglobin per 100 mL of blood or a hematocrit value of 33 percent.

(4) Freedom from acute respiratory diseases;

(5) Freedom from any infectious skin disease at the site of phlebotomy and from any such disease generalized to such an extent as to create a risk of contamination of the blood;

(6) Freedom from any disease transmissible by blood transfusion, insofar as can be determined by history and examinations indicated above; and

(7) Freedom of the arms and forearms from skin punctures or scars indicative of addiction to self-injected narcotics.

(c) *Additional qualifications of donor; viral hepatitis.* No individual shall be used as a source of Whole Blood if he has—

(1) A history of viral hepatitis after the 11th birthday;

(2) A history of close contact within 12 months of donation with an individual having viral hepatitis;

(3) A history of having received within 12 months of donation, human blood or any derivative of human blood which the Food and Drug Administration has advised the blood establishment is a possible source of viral hepatitis.

(d) *Therapeutic bleedings.* Blood withdrawn in order to promote the health of a donor otherwise qualified under the provisions of this section, shall not be used as a source of Whole Blood unless the container label conspicuously indicates the donor's disease that necessitated withdrawal of blood.

(e) [Reserved]

(f) *Qualifications; donations within less than 8 weeks.* A person may serve as a source of Whole Blood more than once in 8 weeks only if at the time of donation the person is examined and certified by a physician to be in good

health, as indicated in part in paragraph (b) of this section.

[38 FR 32089, Nov. 20, 1973, as amended at 49 FR 23834, June 8, 1984; 50 FR 4138, Jan. 29, 1985; 51 FR 15611, Apr. 25, 1986; 55 FR 11013, Mar. 26, 1990; 64 FR 45371, Aug. 19, 1999; 66 FR 1836, Jan. 10, 2001; 66 FR 40889, Aug. 6, 2001]

§ 640.4 Collection of the blood.

(a) *Supervision.* Blood shall be drawn from the donor by a qualified physician or under his supervision by assistants trained in the procedure. A physician shall be present on the premises when blood is being collected, except that blood may be collected when a physician is not present on the premises, provided the establishment (1) maintains on the premises, and files with the Center for Biologics Evaluation and Research, a manual of standard procedures and methods, approved by the Director of the Center for Biologics Evaluation and Research, that shall be followed by employees who collect blood, and (2) maintains records indicating the name and qualifications of the person immediately in charge of the employees who collect blood when a physician is not present on the premises.

(b) *The donor center.* The pertinent requirements of §§ 600.10 and 600.11 of this chapter shall apply at both the blood establishment and at any other place where the bleeding is performed.

(c) *Blood containers.* Blood containers and donor sets shall be pyrogen-free, sterile and identified by lot number. The amount of anticoagulant required for the quantity of blood to be collected shall be in the blood container when it is sterilized. In addition, all container and donor set surfaces that come in contact with blood used in the processing of Heparin Whole Blood shall be water repellent.

(d) *The anticoagulant solution.* The anticoagulant solution shall be sterile and pyrogen-free. Anticoagulant solutions shall be compounded and used according to a formula approved by the Director, Center for Biologics Evaluation and Research.

(e) *Donor identification.* Each unit of blood shall be so marked or identified by number or other symbol as to relate it to the individual donor whose identity shall be established to the extent necessary for compliance with § 640.3.

(f) *Prevention of contamination of the blood.* The skin of the donor at the site of phlebotomy shall be prepared thoroughly and carefully by a method that gives maximum assurance of a sterile container of blood. The blood shall be collected by aseptic methods in a sterile system which may be closed or may be vented if the vent protects the blood against contamination.

(g) *Samples and segments for laboratory tests.* Samples and segments for laboratory tests shall meet the following standards:

(1) One or more segments shall be provided with each unit of blood when issued or reissued except as provided in § 640.2(c)(2) and all segments shall be from the donor who is the source of the unit of blood.

(2) All samples for laboratory tests performed by the manufacturer and all segments accompanying a unit of blood shall be collected at the time of filling the original blood container.

(3) All containers for all samples shall bear the donor's identification before collecting the samples.

(4) All segments accompanying a unit of blood shall be attached to the whole blood container before blood collection, in a tamperproof manner that will conspicuously indicate removal and reattachment.

(5) Segments for compatibility testing shall contain blood mixed with the appropriate anticoagulant.

(h) *Storage.* Whole Blood must be placed in storage at a temperature between 1 and 6 °C immediately after collection unless the blood is to be further processed into another component or the blood must be transported from the donor center to the processing laboratory. If transported, the blood must be placed in temporary storage having sufficient refrigeration capacity to cool the blood continuously toward a temperature range between 1 and 10 °C until arrival at the processing laboratory. At the processing laboratory, the blood must be stored at a temperature between 1 and 6 °C. Blood from which a component is to be prepared must be held in an environment maintained at a temperature range specified for that component in the directions for use for

the blood collecting, processing, and storage system approved for such use by the Director, CBER.

[38 FR 32089, Nov. 20, 1973, as amended at 42 FR 59878, Nov. 22, 1977; 43 FR 34460, Aug. 4, 1978; 49 FR 23834, June 8, 1984; 50 FR 4138, Jan. 29, 1985; 55 FR 11013, Mar. 26, 1990; 64 FR 45372, Aug. 19, 1999; 66 FR 1836, Jan. 10, 2001; 66 FR 40889, Aug. 6, 2001; 72 FR 45887, Aug. 16, 2007; 73 FR 7464, Feb. 8, 2008]

§ 640.5 Testing the blood.

All laboratory tests shall be made on a specimen of blood taken from the donor at the time of collecting the unit of blood, and these tests shall include the following:

(a) *Serological test for syphilis.* Whole Blood shall be negative to a serological test for syphilis.

(b) *Determination of blood group.* Each container of Whole Blood shall be classified as to ABO blood group. At least two blood group tests shall be made and the unit shall not be issued until grouping tests by different methods or with different lots of antiserums are in agreement. Only those Anti-A and Anti-B Blood Grouping Reagents licensed under, or that otherwise meet the requirements of, the regulations of this subchapter shall be used, and the technique used shall be that for which the serum is specifically designed to be effective.

(c) *Determination of the Rh factors.* Each container of Whole Blood shall be classified as to Rh type on the basis of tests done on the sample. The label shall indicate the extent of typing and the results of all tests performed. If the test, using Anti-D Blood Grouping Reagent, is positive, the container may be labeled "Rh Positive." If the test is negative, the results shall be confirmed by further testing which shall include tests for the "weak D (formerly D^u)." Blood may be labeled "Rh Negative" if further testing is negative. Units testing positive after additional more specific testing shall be labeled as "Rh Positive." Only Anti-Rh Blood Grouping Reagents licensed under, or that otherwise meet the requirements of, this subchapter shall be used, and the technique used shall be that for which the reagent is specifically designed to be effective.

(d) *Sterility test.* Whole Blood intended for transfusion shall not be tested for sterility by a method that entails entering the final container before the blood is used for transfusion.

(e) *Inspection.* Whole Blood shall be inspected visually during storage and immediately prior to issue. If the color or physical appearance is abnormal or there is any indication or suspicion of microbial contamination the unit of Whole Blood shall not be issued for transfusion.

(f) *Test for communicable disease agents.* Whole Blood shall be tested for evidence of infection due to communicable disease agents as required under § 610.40 of this chapter.

[38 FR 32089, Nov. 20, 1973, as amended at 50 FR 4138, Jan. 29, 1985; 53 FR 117, Jan. 5, 1988; 53 FR 12764, Apr. 19, 1988; 64 FR 45372, Aug. 19, 1999; 66 FR 1836, Jan. 10, 2001; 66 FR 31165, June 11, 2001; 66 FR 40889, Aug. 6, 2001]

§ 640.6 Modifications of Whole Blood.

Upon approval by the Director, Center for Biologics Evaluation and Research, of a supplement to the biologics license application for Whole Blood a manufacturer may prepare Whole Blood from which the antihemophilic factor has been removed, provided the Whole Blood meets the applicable requirements of this subchapter and the following conditions are met:

(a) The antihemophilic factor shall be removed in accordance with paragraphs (a), (b), and (c) of § 640.52.

(b) Although the closed system between the red blood cells and plasma shall be maintained, the red blood cells shall be maintained between 1 and 6 °C at all times, including that time when the plasma is being frozen for removal of the antihemophilic factor.

[38 FR 32089, Nov. 20, 1973, as amended at 49 FR 23834, June 8, 1984; 50 FR 4138, Jan. 29, 1985; 55 FR 11013, Mar. 26, 1990; 59 FR 49351, Sept. 28, 1994; 64 FR 45372, Aug. 19, 1999; 64 FR 56453, Oct. 20, 1999]

Subpart B—Red Blood Cells

§ 640.10 Red Blood Cells.

The proper name of this product shall be Red Blood Cells. The product is defined as red blood cells remaining after separating plasma from human blood.

[38 FR 32089, Nov. 20, 1973, as amended at 50 FR 4138, Jan. 29, 1985]

§ 640.11 General requirements.

(a) *Storage.* Immediately after processing, the Red Blood Cells shall be placed in storage and maintained at a temperature between 1 and 6 °C.

(b) *Inspection.* The product shall be inspected immediately after separation of the plasma, periodically during storage, and at the time of issue. The product shall not be issued if there is any abnormality in color or physical appearance or if there is any indication of microbial contamination.

[38 FR 32089, Nov. 20, 1973, as amended at 41 FR 18292, May 3, 1976; 42 FR 59878, Nov. 11, 1977; 50 FR 4139, Jan. 29, 1985]

§ 640.12 Suitability of donor.

The source blood for Red Blood Cells shall be obtained from a donor who meets the criteria for donor suitability prescribed in § 640.3.

[38 FR 32089, Nov. 20, 1973, as amended at 50 FR 4139, Jan. 29, 1985]

§ 640.13 Collection of the blood.

(a) The source blood shall be collected as prescribed in § 640.4.

(b) Source blood may also be derived from Whole Blood manufactured in accordance with applicable provisions of this subchapter.

[38 FR 32089, Nov. 20, 1973, as amended at 50 FR 4139, Jan. 29, 1985; 64 FR 45372, Aug. 19, 1999]

§ 640.14 Testing the blood.

Blood from which Red Blood Cells are prepared shall be tested as prescribed in § 610.40 of this chapter and § 640.5 (a), (b), and (c).

[53 FR 117, Jan. 5, 1988, as amended at 66 FR 31165, June 11, 2001]

§ 640.15 Segments for testing.

Segments collected in integral tubing shall meet the following standards:

(a) One or more segments shall be provided with each unit of Whole Blood or Red Blood Cells when issued or reissued.

(b) Before they are filled, all segments shall be marked or identified so as to relate them to the donor of that unit of red cells.

(c) All segments accompanying a unit of Red Blood Cells shall be filled at the time the blood is collected or at the time the final product is prepared.

[66 FR 40890, Aug. 6, 2001]

§ 640.16 Processing.

(a) *Separation.* Within the timeframe specified in the directions for use for the blood collecting, processing, and storage system used, Red Blood Cells may be prepared either by centrifugation, done in a manner that will not tend to increase the temperature of the blood, or by normal undisturbed sedimentation. A portion of the plasma sufficient to insure optimal cell preservation shall be left with the red cells except when a cryoprotective substance or additive solution is added for prolonged storage.

(b) *Sterile system.* All surfaces that come in contact with the red cells shall be sterile and pyrogen-free.

(c) *Final containers.* Final containers used for Red Blood Cells shall be the original blood containers unless the method of processing requires a different container. The final container shall meet the requirements for blood containers prescribed in § 640.2(c). At the time of filing, if a different container is used, it shall be marked or identified by number or other symbol so as to relate it to the donor of that unit of red cells.

[38 FR 32089, Nov. 20, 1973, as amended at 43 FR 34460, Aug. 4, 1978; 50 FR 4139, Jan. 29, 1985; 64 FR 45372, Aug. 19, 1999; 66 FR 1836, Jan. 10, 2001; 66 FR 40890, Aug. 6, 2001]

§ 640.17 Modifications for specific products.

Red Blood Cells Frozen: A cryophylactic substance may be added to the Red Blood Cells for extended manufacturers' storage at −65 °C or colder, provided the manufacturer submits data considered by the Director, Center for Biologics Evaluation and Research, as adequately demonstrating

through in vivo cell survival and other appropriate tests that the addition of the substance, the materials used and the processing methods results in a final product that meets the required standards of safety, purity, and potency for Red Blood Cells, and that the frozen product will maintain those properties for the prescribed dating period. Section 640.11 (a) and (b) do not apply while a cryophylactic substance is present.

[38 FR 32089, Nov. 20, 1973, as amended at 41 FR 18292, May 3, 1976; 49 FR 23834, June 8, 1984; 50 FR 4139, Jan. 29, 1985; 55 FR 11013, Mar. 26, 1990; 63 FR 16685, Apr. 6, 1998]

Subpart C—Platelets

§ 640.20 Platelets.

(a) *Proper name and definition.* The proper name of this product shall be Platelets. The product is defined as platelets collected from one unit of blood and resuspended in an appropriate volume of original plasma, as prescribed in § 640.24(d).

(b) *Source.* The source material for Platelets is plasma which may be obtained by whole blood collection or by plateletpheresis.

[40 FR 4304, Jan. 29, 1975, as amended at 47 FR 49021, Oct. 29, 1982; 50 FR 4139, Jan. 29, 1985; 72 FR 45887, Aug. 16, 2007]

§ 640.21 Suitability of donors.

(a) Whole blood donors shall meet the criteria for suitability prescribed in § 640.3.

(b) [Reserved]

(c) Plateletpheresis donors must meet the criteria for suitability as prescribed in §§ 640.3 and 640.63(c)(6) or as described in an approved biologics license application (BLA) or an approved supplement to a BLA. Informed consent must be obtained as prescribed in § 640.61.

[40 FR 4304, Jan. 29, 1975, as amended at 49 FR 23834, June 8, 1984; 64 FR 56453, Oct. 20, 1999; 72 FR 45887, Aug. 16, 2007]

§ 640.22 Collection of source material.

(a) Whole blood used as the source of Platelets shall be collected as prescribed in § 640.4.

(b) [Reserved]

(c) If plateletpheresis is used, the procedure for collection must be as prescribed in §§ 640.62, 640.64 (except paragraph (c)), and 640.65, or as described in an approved biologics license application (BLA) or an approved supplement to a BLA.

(d) The phlebotomy shall be performed by a single uninterrupted venipuncture with minimal damage to, and minimal manipulation of, the donor's tissue.

[40 FR 4304, Jan. 29, 1975, as amended at 45 FR 27927, Apr. 25, 1980; 49 FR 23834, June 8, 1984; 50 FR 4139, Jan. 29, 1985; 55 FR 11013, Mar. 26, 1990; 59 FR 49351, Sept. 28, 1994; 64 FR 45372, Aug. 19, 1999; 64 FR 56453, Oct. 20, 1999; 72 FR 45887, Aug. 16, 2007]

§ 640.23 Testing the blood.

(a) Blood from which plasma is separated for the preparation of Platelets shall be tested as prescribed in § 610.40 of this chapter and § 640.5 (a), (b), and (c).

(b) The tests shall be performed on a sample of blood collected at the time of collecting the source blood, and such sample container shall be labeled with the donor's number before the container is filled.

[40 FR 4304, Jan. 29, 1975, as amended at 50 FR 4139, Jan. 29, 1985; 53 FR 117, Jan. 5, 1988; 64 FR 45372, Aug. 19, 1999; 66 FR 1836, Jan. 10, 2001; 66 FR 31165, June 11, 2001]

§ 640.24 Processing.

(a) Separation of plasma and platelets and resuspension of the platelets must be in a closed system. Platelets must not be pooled during processing unless the platelets are pooled as specified in the directions for use for the blood collecting, processing, and storage system approved for such use by the Director, Center for Biologics Evaluation and Research.

(b) Immediately after collection, the whole blood or plasma shall be held in storage between 20 and 24 °C unless it must be transported from the collection center to the processing laboratory. During such transport, all reasonable methods shall be used to maintain the temperature as close as possible to a range between 20 and 24 °C until it arrives at the processing laboratory where it shall be held between 20 and 24 °C until the platelets are separated.

The platelet concentrate shall be separated within 4 hours or within the timeframe specified in the directions for use for the blood collecting, processing, and storage system.

(c) The time and speed of centrifugation must have been demonstrated to produce an unclumped product, without visible hemolysis, that yields a count of not less than 5.5×10^{10} platelets per unit in at least 75 percent of the units tested.

(d) The volume of original plasma used for resuspension of the platelets shall be determined by the maintenance of a pH of not less than 6.2 during the storage period. The pH shall be measured on a sample of platelets which has been stored for the maximum dating period at the selected storage temperature. One of the following storage temperatures shall be used continuously:

(1) 20 to 24 °C.

(2) 1 to 6 °C.

(e) Final containers used for Platelets shall be colorless and transparent to permit visual inspection of the contents; any closure shall maintain a hermetic seal and prevent contamination of the contents. The container material shall not interact with the contents, under the customary conditions of storage and use, in such a manner as to have an adverse effect upon the safety, purity, potency, or efficacy of the product. At the time of filling, the final container shall be marked or identified by number so as to relate it to the donor.

[40 FR 4304, Jan. 29, 1975, as amended at 42 FR 10983, Feb. 25, 1977; 47 FR 49021, Oct. 29, 1982; 50 FR 4139, Jan. 29, 1985; 63 FR 16685, Apr. 6, 1998; 64 FR 45872, Aug. 19, 1999; 66 FR 1836, Jan. 10, 2001; 66 FR 40890, Aug. 6, 2001; 72 FR 45887, Aug. 16, 2007; 73 FR 7464, Feb. 8, 2008]

§ 640.25 General requirements.

(a) *Storage.* Immediately after resuspension, Platelets shall be placed in storage at the selected temperature range. If stored at 20 to 24 °C, a continuous gentle agitation of the platelet concentrate shall be maintained throughout the storage period. Agitation is optional if stored at a temperature between 1 and 6 °C.

(b) *Quality control testing.* Each month four units prepared from different donors shall be tested at the end of the storage period as follows:

(1) Platelet count.

(2) pH of not less than 6.2 measured at the storage temperature of the unit.

(3) Measurement of actual plasma volume.

(4) If the results of the quality control testing indicate that the product does not meet the prescribed requirements, immediate corrective action shall be taken and a record maintained of such action.

(c) *Manufacturing responsibility.* All manufacturing of Platelets shall be performed at the same licensed establishment, except that the quality control testing under paragraph (b) of this section may be performed by a clinical laboratory which meets the standards of the Clinical Laboratories Improvement Amendments of 1988 (CLIA) (42 U.S.C. 263a) and is qualified to perform platelet counts. Such arrangements must be approved by the Director, Center for Biologics Evaluation and Research, Food and Drug Administration. Such testing shall not be considered as divided manufacturing, as described in § 610.63 of this chapter, provided the following conditions are met:

(1) The results of each test are received within 10 days of the preparation of the platelet concentrate, and are maintained by the establishment licensed for Platelets so that they may be reviewed by an authorized representative of the Food and Drug Administration.

(2) The licensed Platelets manufacturer has obtained a written agreement that the testing laboratory will permit an authorized representative of the Food and Drug Administration to inspect its testing procedures and facilities during reasonable business hours.

(3) The testing laboratory will participate in any proficiency testing programs undertaken by the Center for Biologics Evaluation and Research, Food and Drug Administration.

[40 FR 4304, Jan. 29, 1975, as amended at 47 FR 49021, Oct. 29, 1982; 49 FR 23834, June 8, 1984; 50 FR 4139, Jan. 29, 1985; 55 FR 11013, Mar. 26, 1990; 66 FR 1836, Jan. 10, 2001; 72 FR 45888, Aug. 16, 2007]

§ 640.27 Emergency provisions.

The use of the plateletpheresis procedure to obtain a product for a specific recipient may be at variance with §§ 640.21(c) and 640.22(c): *Provided*, That: (a) A licensed physician has determined that the recipient must be transfused with the platelets from a specific donor, and (b) the plateletpheresis procedure is performed under the supervision of a qualified licensed physician who is aware of the health status of the donor and the physician has certified in writing that the donor's health permits plateletpheresis.

[40 FR 53544, Nov. 18, 1975]

Subpart D—Plasma

§ 640.30 Plasma.

(a) *Proper name and definition.* The proper name of this component is Plasma. The component is defined as:

(1) The fluid portion of one unit of human blood intended for intravenous use which is collected in a closed system, stabilized against clotting, and separated from the red cells; or

(2) The fluid portion of human blood intended for intravenous use which is prepared by apheresis methods as specified in the directions for use for the blood collecting, processing, and storage system including closed and open systems.

(b) *Source.* (1) Plasma shall be obtained by separating plasma from blood collected from blood donors or by plasmapheresis.

(2) Plasma may be obtained from a unit of Whole Blood collected by another licensed establishment.

[42 FR 59878, Nov. 22, 1977; 48 FR 13026, Mar. 29, 1983, as amended at 50 FR 4139, Jan. 29, 1985; 72 FR 45888, Aug. 16, 2007]

§ 640.31 Suitability of donors.

(a) Whole blood donors shall meet the criteria for donor suitability prescribed in § 640.3.

(b) Plasmapheresis donors shall meet the criteria for donor suitability prescribed in § 640.63, excluding the phrase "other than malaria" in paragraph (c)(9) of that section. Informed consent shall be required as prescribed in § 640.61.

[42 FR 59878, Nov. 22, 1977, as amended at 64 FR 45372, Aug. 19, 1999]

§ 640.32 Collection of source material.

(a) Whole Blood must be collected, transported, and stored as prescribed in § 640.4. When whole blood is intended for Plasma, Fresh Frozen Plasma, and Liquid Plasma, until the plasma is removed, the whole blood must be maintained at a temperature between 1 and 6 °C or as specified in the directions for use for the blood collecting, processing, and storage system approved for such use by the Director, Center for Biologics Evaluations and Research. Whole blood intended for Platelet Rich Plasma must be maintained as prescribed in § 640.24 until the plasma is removed. The red blood cells must be placed in storage at a temperature between 1 and 6 °C immediately after the plasma is separated.

(b) Plasma obtained by plasmapheresis shall be collected as prescribed in §§ 640.62, 640.64 (except that paragraph (c)(3) of § 640.64 shall not apply), and § 640.65.

[42 FR 59878, Nov. 22, 1977, as amended at 45 FR 27927, Apr. 25, 1980; 50 FR 4139, Jan. 29, 1985; 64 FR 45372, Aug. 19, 1999; 72 FR 45888, Aug. 16, 2007]

§ 640.33 Testing the blood.

(a) Blood from which plasma is separated shall be tested as prescribed in § 610.40 of this chapter and § 640.5 (a), (b), and (c).

(b) Manufacturers of Plasma collected by plasmapheresis shall have testing and recordkeeping responsibilities equivalent to those prescribed in §§ 640.71 and 640.72.

[42 FR 59878, Nov. 22, 1977, as amended at 44 FR 17658, Mar. 23, 1979; 50 FR 4136, Jan. 29, 1985; 53 FR 117, Jan. 5, 1988; 66 FR 31165, June 11, 2001]

§ 640.34 Processing.

(a) *Plasma.* Plasma shall be separated from the red blood cells and shall be stored at -18 °C or colder within 6 hours after transfer to the final container or within the timeframe specified in the directions for use for the blood collecting, processing, and storage system

unless the product is to be stored as Liquid Plasma.

(b) *Fresh Frozen Plasma.* Fresh frozen plasma shall be prepared from blood collected by a single uninterrupted venipuncture with minimal damage to and minimal manipulation of the donor's tissue. The plasma must be separated from the red blood cells or collected by an apheresis procedure, and placed in a freezer within 8 hours or within the timeframe specified in the directions for use for the blood collecting, processing, and storage system, and stored at -18 °C or colder.

(c) *Liquid Plasma.* Liquid Plasma shall be separated from the red blood cells and shall be stored at a temperature of 1 to 6 °C within 4 hours after filling the final container or within the timeframe specified in the directions for use for the blood collecting, processing, and storage system.

(d) *Platelet Rich Plasma.* Platelet rich plasma shall be prepared from blood collected by a single uninterrupted venipuncture with minimal damage to and manipulation of the donor's tissue. The plasma shall be separated from the red blood cells by centrifugation within 4 hours after completion of the phlebotomy or within the timeframe specified in the directions for use for the blood collecting, processing, and storage system. The time and speed of the centrifugation shall have been shown to produce a product with at least 250,000 platelets per microliter. The plasma shall be stored at a temperature between 20 and 24 °C immediately after filling the final container. A gentle and continuous agitation of the product shall be maintained throughout the storage period, if stored at a temperature of 20 to 24 °C.

(e) *Modifications of Plasma.* It is possible to separate Platelets and/or Cryoprecipitated AHF from Plasma. When these components are to be separated, the plasma shall be collected as described in § 640.32 for Plasma.

(1) Platelets shall be separated as prescribed in subpart C of part 640, prior to freezing the plasma. The remaining plasma may be labeled as "Fresh Frozen Plasma," if frozen within 6 hours after filling the final container or within the timeframe specified in the directions for use for the blood collecting, processing, and storage system.

(2) Cryoprecipitated AHF shall be removed as prescribed in subpart F of part 640. The remaining plasma shall be labeled "Plasma, Cryoprecipitate Reduced."

(3) Plasma remaining after both Platelets and Cryoprecipitated AHF have been removed may be labeled "Plasma, Cryoprecipitate Reduced."

(f) *The final container.* (1) The final container shall have no color added to the plastic and shall be transparent to permit visual inspection of the contents; any closure shall maintain a hermetic seal and prevent contamination of the contents.

(2) The final container material shall not interact with the contents, under the customary conditions of storage and use, in such a manner as to have an adverse effect upon the safety, purity, potency, and effectiveness of the product.

(3) Prior to filling, the final container shall be identified by number so as to relate it to the donor.

(g) *The final product.* (1) The final product shall be inspected immediately after separation of the plasma and shall not be issued for transfusion if there is (i) any abnormality in color or physical appearance, or (ii) any indication of contamination.

(2) With the exception of Platelet Rich Plasma and Liquid Plasma the final product shall be inspected for evidence of thawing or breakage at the time of issuance, however, the containers need not be stored in a manner that shows evidence of thawing if records of continuous monitoring of the storage temperature establish that the temperature remained at –18 °C or colder. If continuous monitoring of the product is not available, the final product shall be stored in a manner that will show evidence of thawing and shall not be issued if there is any evidence of thawing.

(3) No preservative shall be added to the final product.

[42 FR 59878, Nov. 22, 1977, as amended at 43 FR 34460, Aug. 4 1978; 48 FR 13026, Mar. 29, 1983; 50 FR 4139, Jan. 29, 1985; 64 FR 45373, Aug. 19, 1999; 66 FR 1836, Jan. 10, 2001; 66 FR 40890, Aug. 6, 2001; 72 FR 45888, Aug. 16, 2007]

Subpart E [Reserved]

Subpart F—Cryoprecipitate

§ 640.50 Cryoprecipitated AHF.

(a) *Proper name and definition.* The proper name of this product shall be Cryoprecipitated AHF. The product is defined as a preparation of antihemophilic factor, which is obtained from a single unit of plasma collected and processed in a closed system.

(b) *Source.* The source material for Cryoprecipitated AHF shall be plasma which may be obtained by whole blood collection or by plasmapheresis.

[42 FR 21774, Apr. 29, 1977; 48 FR 13026, Mar. 29, 1983; as amended at 50 FR 4139, Jan. 29, 1985]

§ 640.51 Suitability of donors.

(a) Whole blood donors shall meet the criteria for suitability prescribed in § 640.3.

(b) Plasmapheresis donors shall meet the criteria for suitability prescribed in § 640.63, excluding the phrase "other than malaria" in paragraph (c) (9) of that section. Informed consent shall be required as prescribed in § 640.61.

[42 FR 21774, Apr. 29, 1977, as amended at 64 FR 45373, Aug. 19, 1999; 73 FR 49942, Aug. 25, 2008]

§ 640.52 Collection of source material.

(a) Whole blood used as a source of Cryoprecipitated AHF shall be collected as prescribed in § 640.4. Whole blood from which both Platelets and Cryoprecipitated AHF is derived shall be maintained as required under § 640.24 until the platelets are removed.

(b) If plasmapheresis is used, the procedure for collection shall be as prescribed in §§ 640.62, 640.64 (except that paragraph (c)(3) of that section shall not apply), and 640.65.

[42 FR 21774, Apr. 29, 1977, as amended at 50 FR 4139, Jan. 29, 1985; 64 FR 45373, Aug. 19, 1999]

§ 640.53 Testing the blood.

(a) Blood from which plasma is separated for the preparation of Cryoprecipitated AHF shall be tested as prescribed in § 610.40 of this chapter and § 640.5 (a), (b), and (c).

(b) The tests shall be performed on a sample of blood collected at the time of collecting the source blood, and such sample container shall be labeled with the donor's number before the container is filled.

(c) Manufacturers of Cryoprecipitated AHF obtained from plasma collected by plasmapheresis shall have testing and record-keeping responsibilities equivalent to those prescribed in §§ 640.71 and 640.72.

[42 FR 21774, Apr. 29, 1977, as amended at 42 FR 37546, July 22, 1977; 42 FR 43063, Aug. 26, 1977; 50 FR 4139, Jan. 29, 1985; 53 FR 117, Jan. 5, 1988; 66 FR 31165, June 11, 2001]

§ 640.54 Processing.

(a) *Processing the plasma.* (1) The plasma shall be separated from the red blood cells by centrifugation to obtain essentially cell-free plasma.

(2) The plasma shall be placed in a freezer within 8 hours after blood collection or within the timeframe specified in the directions for use for the blood collecting, processing, and storage system. A combination of dry ice and organic solvent may be used for freezing: *Provided,* That the procedure has been shown not to cause the solvent to penetrate the container or leach plasticizer from the container into the plasma.

(3) Immediately after separation and freezing of the plasma, the plasma shall be stored and maintained at −18 °C or colder until thawing of the plasma for further processing to remove the Cryoprecipitated AHF.

(b) *Processing the final product.* (1) The Cryoprecipitated AHF shall be separated from the plasma by a procedure that has been shown to produce an average of no less than 80 units of antihemophilic factor per final container.

(2) No diluent shall be added to the product by the manufacturer prior to freezing.

(3) The final container used for Cryoprecipitated AHF shall be colorless and transparent to permit visual inspection of the contents; any closure shall maintain a hermetic seal and prevent contamination of the contents. The container material shall not interact with the contents under customary conditions of storage and use in such a

manner as to have an adverse effect upon the safety, purity, potency and effectiveness of the product. At the time of filling, the final container shall be identified by a number so as to relate it to the donor.

[42 FR 21774, Apr. 29, 1977, as amended at 47 FR 15330, Apr. 9, 1982; 50 FR 4139, Jan. 29, 1985; 64 FR 45373, Aug. 19, 1999; 66 FR 1837, Jan. 10, 2001; 66 FR 40890, Aug. 6, 2001]

§ 640.55 U.S. Standard preparation.

A U.S. Standard Antihemophilic Factor (Factor VIII) preparation may be obtained from the Center for Biologics Evaluation and Research, (HFM–407) (see mailing addresses in § 600.2 of this chapter) for use in the preparation of a working reference to be employed in a quality control potency test of Cryoprecipitated AHF.

[42 FR 21774, Apr. 29, 1977, as amended at 49 FR 23834, June 8, 1984; 50 FR 4140, Jan. 29, 1985; 55 FR 11013, Mar. 26, 1990; 70 FR 14985, Mar. 24, 2005]

§ 640.56 Quality control test for potency.

(a) Quality control tests for potency of antihemophilic factor shall be conducted each month on at least four representative containers of Cryoprecipitated AHF.

(b) The results of each test are received by the establishment licensed for Cryoprecipitated AHF within 30 days of the preparation of the cryoprecipitated antihemophilic factor and are maintained at that establishment so that they may be reviewed by an authorized representative of the Food and Drug Administration.

(c) The quality control test for potency may be performed by a clinical laboratory which meets the standards of the Clinical Laboratories Improvement Amendments of 1988 (CLIA) (42 U.S.C. 263a) and is qualified to perform potency tests for antihemophilic factor. Such arrangements must be approved by the Director, Center for Biologics Evaluation and Research, Food and Drug Administration. Such testing shall not be considered as divided manufacturing, as described in § 610.63 of this chapter, provided the following conditions are met:

(1) The establishment licensed for Cryoprecipitated AHF has obtained a written agreement that the testing laboratory will permit an authorized representative of the Food and Drug Administration to inspect its testing procedures and facilities during reasonable business hours.

(2) The testing laboratory will participate in any proficiency testing programs undertaken by the Center for Biologics Evaluation and Research, Food and Drug Administration.

(d) If the average potency level of antihemophilic factor in the containers tested is less than 80 units of antihemophilic factor per container, immediate corrective actions shall be taken and a record maintained of such action.

[42 FR 21774, Apr. 29, 1977, as amended at 49 FR 23834, June 8, 1984; 50 FR 4140, Jan. 29, 1985; 55 FR 11013, Mar. 26, 1990; 64 FR 45373, Aug. 19, 1999; 66 FR 1837, Jan. 10, 2001]

Subpart G—Source Plasma

§ 640.60 Source Plasma.

The proper name of the product shall be Source Plasma. The product is defined as the fluid portion of human blood collected by plasmapheresis and intended as source material for further manufacturing use. The definition excludes single donor plasma products intended for intravenous use.

[41 FR 10768, Mar. 12, 1976, as amended at 50 FR 4140, Jan. 29, 1985]

§ 640.61 Informed consent.

The written consent of a prospective donor shall be obtained after a qualified licensed physician has explained the hazards of the procedure to the prospective donor. The explanation shall include the risks of a hemolytic transfusion reaction if he is given the cells of another donor, and the hazards involved if he is hyperimmunized. The explanation shall consist of such disclosure and be made in such a manner that intelligent and informed consent be given and that a clear opportunity to refuse is presented.

§ 640.62 Medical supervision.

A qualified licensed physician shall be on the premises when donor suitability is being determined, immunizations are being made, whole blood is

being collected, and red blood cells are being returned to the donor.

[66 FR 1837, Jan. 10, 2001]

§ 640.63 Suitability of donor.

(a) *Method of determining.* The suitability of a donor for Source Plasma shall be determined by a qualified licensed physician or by persons under his supervision and trained in determining donor suitability. Such determination shall be made on the day of collection from the donor by means of a medical history, tests, and such physical examination as appears necessary to the qualified licensed physician.

(b) *Initial medical examinations.* (1) Each donor shall be examined by a qualified licensed physician on the day of the first donation or no more than 1 week before the first donation and at subsequent intervals of no longer than 1 year.

(2)(i) A donor who is to be immunized for the production of high-titer plasma shall be examined by a qualified licensed physician. The medical examination shall be performed within no more than 1 week before the first immunization injection. The medical examination for plasmapheresis need not be repeated, if the first donation occurs within 3 weeks after the first injection.

(ii) A donor who is an active participant in a plasmapheresis program, and has been examined in accordance with paragraph (b)(1) of this section, need not be reexamined before immunization for the production of high-titer plasma.

(3) Each donor shall be certified to be in good health by the examining physician. The certification of good health shall be on a form supplied by the licensed establishment and shall indicate that the certification applies to the suitability of the individual to be a plasmapheresis donor and, when applicable, an immunized donor.

(c) *Qualification of donor.* Donors shall be in good health on the day of donation, as indicated in part by:

(1) Normal temperature;

(2) Demonstration that systolic and diastolic blood pressures are within normal limits, unless the examining physician is satisfied that an individual with blood pressures outside these limits is an otherwise qualified donor under the provisions of this section;

(3) A blood hemoglobin level of no less than 12.5 grams of hemoglobin per 100 milliliters of blood or a hematocrit level of 38 percent;

(4) A normal pulse rate;

(5) A total serum or total plasma protein of no less than 6.0 grams per 100 milliliters of blood;

(6) Weight, which shall be at least 110 pounds;

(7) Freedom from acute respiratory diseases;

(8) Freedom from any infectious skin disease at the site of phlebotomy and from any such disease generalized to such an extent as to create a risk of contamination of the plasma;

(9) Freedom from any disease, other than malaria, transmissible by blood transfusion, insofar as can be determined by history and examinations indicated in this section;

(10) Freedom of the arms and forearms from skin punctures or scars indicative of addiction to self-injected narcotics;

(11) Freedom from a history of viral hepatitis after the 11th birthday;

(12) Freedom from a history of close contact within 12 months of donation with an individual having viral hepatitis;

(13) Freedom from a history of having received, within 12 months, human blood or any derivative of human blood which the Food and Drug Administration has advised the blood establishment is a possible source of viral hepatitis, except for specific immunization performed in accordance with § 640.66.

(d) *General.* Any donor who, in the opinion of the interviewer, appears to be under the influence of any drug, alcohol, or for any reason does not appear to be providing reliable answers to medical history questions, shall not be considered a suitable donor.

(e) *Failure to return red blood cells.* Any donor who has not had the red blood cells returned from a unit of blood collected during a plasmapheresis procedure or who has been a donor of a unit of whole blood shall not be subjected to plasmapheresis for a period of 8 weeks, unless:

(1) The donor has been examined by a qualified licensed physician and certified by the physician to be acceptable for further plasmapheresis before expiration of the 8-week period;

(2) The donor possesses an antibody that is (i) transitory, (ii) of a highly unusual or infrequent specificity, or (iii) of an unusually high titer; and

(3) The special characteristics of the antibody and the need for plasmapheresing the donor are documented.

[38 FR 32089, Nov. 20, 1973, as amended at 41 FR 10768, Mar. 12, 1976; 43 FR 9805, Mar. 10, 1978; 43 FR 12311, Mar. 24, 1978; 46 FR 57480, Nov. 24, 1981; 50 FR 4140, Jan. 29, 1985; 64 FR 45373, Aug. 19, 1999; 66 FR 1837, Jan. 10, 2001; 66 FR 40890, Aug. 6, 2001]

§ 640.64 Collection of blood for Source Plasma.

(a) *Supervision.* All blood for the collection of Source Plasma shall be drawn from the donor by a qualified licensed physician or by persons under his supervision trained in the procedure.

(b) *Blood containers.* Blood containers and donor sets must be pyrogen-free, sterile, and identified by lot number.

(c) *The anticoagulant solution.* The anticoagulant solution must be sterile and pyrogen-free. Anticoagulant solutions must be compounded and used according to a formula that has been approved for the applicant by the Director, Center for Biologics Evaluation and Research.

(d) *Donor identification.* Each unit of blood and plasma shall be so marked or identified by number or other symbol so as to relate it directly to the donor.

(e) *Prevention of contamination of the blood and plasma.* The skin of the donor at the site of phlebotomy shall be prepared thoroughly and carefully by a method that gives maximum assurance of a sterile container of blood. The blood shall be collected, the plasma separated, and the cells returned to the donor by aseptic methods in a sterile system which may be closed, or may be vented if the vent protects the blood cells and plasma against contamination.

[38 FR 32089, Nov. 20, 1973; 39 FR 13632, Apr. 16, 1974, as amended at 41 FR 10768, Mar. 12, 1976; 49 FR 23834, June 8, 1984; 50 FR 4140, Jan. 29, 1985; 55 FR 11013, Mar. 26, 1990; 59 FR 49351, Sept. 28, 1994; 63 FR 16685, Apr. 6, 1998; 64 FR 56453, Oct. 20, 1999; 72 FR 45888, Aug. 16, 2007]

§ 640.65 Plasmapheresis.

(a) *Procedure-general.* The plasmapheresis procedure is a procedure in which, during a single visit to the establishment, blood is removed from a donor, the plasma separated from the formed elements, and at least the red blood cells returned to the donor. This procedure shall be described in detail in the biologics license application.

(b) *Procedures-specific requirements.* The plasmapheresis procedure shall meet the following requirements:

(1)(i) A sample of blood shall be drawn from each donor on the day of the first medical examination or plasmapheresis, whichever comes first and at least every 4 months thereafter by a qualified licensed physician or by persons under his supervision and trained in such procedure. A serologic test for syphilis, a total plasma or serum protein determination, and a plasma or serum protein electrophoresis or quantitative immuno-diffusion test or an equivalent test to determine immunoglobulin composition of the plasma or serum shall be performed on the sample.

(ii) A repeat donor who does not return for plasmapheresis at the time the 4-month sample is due to be collected may be plasmapheresed on the day he appears: *Provided,* That no longer than 6 months has elapsed since the last sample was collected, and the physician on the premises approves the plasmapheresis procedure and so indicates by signing the donor's record before such procedure is performed. The sample for the 4-month tests shall be collected on the day of the donor's return.

(iii) A repeat donor from whom the plasmapheresis center is unable to obtain a sample for testing as prescribed in paragraph (b)(1)(i) of this section for a total period exceeding 6 months shall be processed as a new donor.

(2)(i) The accumulated laboratory data, including tracings, if any, of the plasma or serum protein electrophoresis pattern, the calculated values of each component, and the collection records shall be reviewed by a qualified licensed physician within 21 days after the sample is drawn to determine whether or not the donor may continue in the program. The review shall be signed by the reviewing physician. If the protein composition is not within normal limits established by the testing laboratory, or if the total protein is less than 6.0 grams per 100 milliliters of samples, the donor shall be removed from the program until these values return to normal.

(ii) A donor with a reactive serologic test for syphilis shall not be plasmapheresed again until the donor's serum is tested and found to be nonreactive to a serologic test for syphilis, except as provided in paragraph (b)(2)(iii) and (iv) of this section.

(iii) A donor whose serum is determined to have a biologic false-positive reaction to a serologic test for syphilis may be plasmapheresed: *Provided,* That the donor's file identifies the serologic test for syphilis and results used to confirm the biologic false-positive reaction and indicates that the physician on the premises has determined the false-positive reaction is not the result of an underlying disorder that would disqualify the donor from participation in the plasmapheresis program. If the serologic test for syphilis is performed at a facility other than the plasmapheresis center, all applicable provisions of § 640.71 shall be met.

(iv) A donor with a reactive serologic test for syphilis may be plasmapheresed only to obtain plasma to be used for further manufacturing into control serum for the serologic test for syphilis: *Provided,* That the physician on the premises approves the donation, the donor's file contains a signed statement from a physician or clinic establishing that treatment for syphilis has been initiated and that continuance in the plasmapheresis program will not interfere with or jeopardize the treatment of the syphilitic donor.

(3) A donor identification system shall be established that positively identifies each donor and relates such donor directly to his blood and its components as well as to his accumulated records and laboratory data. Such system shall include either a photograph of each donor which shall be used on each visit to confirm the donor's identity, or some other method that provides equal or greater assurance of positively identifying the donor.

(4) The amount of whole blood, not including anticoagulant, removed from a donor during a manual plasmapheresis procedure or in any 2-day period shall not exceed 1,000 milliliters unless the donor's weight is 175 pounds or greater, in which case the amount of whole blood, not including anticoagulant, removed from the donor during a manual plasmapheresis procedure or in any 2-day period shall not exceed 1,200 milliliters.

(5) The amount of whole blood, not including anticoagulant, removed from a donor during a manual plasmapheresis procedure within a 7-day period shall not exceed 2,000 milliliters unless the donor's weight is 175 pounds or greater, in which case the amount of whole blood, not including anticoagulant, removed from a donor during a manual plasmapheresis procedure within a 7-day period shall not exceed 2,400 milliliters.

(6) No more than 500 milliliters of whole blood shall be removed from a donor at one time, unless the donor's weight is 175 pounds or greater, in which case no more than 600 milliliters of whole blood shall be removed from the donor at one time.

(7) The plasma shall be separated from the red blood cells immediately after blood collection. The maximum feasible volume of red blood cells shall be returned to the donor before another unit is collected.

(8) The volume of plasma collected during an automated plasmapheresis collection procedure shall be consistent with the volumes specifically approved by the Director, Center for Biologics Evaluation and Research, and collection shall not occur less than 2 days apart or more frequently than twice in a 7-day period.

[38 FR 32089, Nov. 20, 1973, as amended at 41 FR 10769, Mar. 12, 1976; 64 FR 45373, Aug. 19, 1999; 64 FR 56453, Oct. 20, 1999]

§ 640.66 Immunization of donors.

If specific immunization of a donor is to be performed, the selection and scheduling of the injection of the antigen, and the evaluation of each donor's clinical response, shall be by a qualified licensed physician or physicians. The administration of the antigen may be performed by a licensed physician or a trained person under his supervision. Any material used for immunization shall be either a product licensed under section 351 of the Public Health Service Act for such purpose or one specifically approved by the Director, Center for Biologics Evaluation and Research, Food and Drug Administration. Immunization procedures shall be on file at each plasmapheresis center where immunizations are performed.

[38 FR 32089, Nov. 20, 1973, as amended at 49 FR 23834, June 8, 1984; 55 FR 11013, Mar. 26, 1990]

§ 640.67 Laboratory tests.

Each unit of Source Plasma shall be tested for evidence of infection due to communicable disease agents as required under § 610.40 of this chapter.

[66 FR 31165, June 11, 2001]

§ 640.68 Processing.

(a) *Sterile system.* All administration and transfer sets inserted into blood containers used for processing Source Plasma intended for manufacturing into injectable or noninjectable products and all interior surfaces of plasma containers used for processing Source Plasma intended for manufacturing into injectable products shall be sterile, pyrogen-free, nontoxic, and compatible with the contents under normal conditions of use. Only Sodium Chloride Injection USP shall be used as a red blood cell diluent. If the method of separation of the plasma intended for injectable products involves a system in which an airway must be inserted into the plasma container, the airway shall be sterile and constructed so as to exclude microorganisms and maintain a sterile system.

(b) *Final containers.* Final containers used for Source Plasma, whether integrally attached or separated from the original blood container, shall not be entered prior to issuance for any purpose except for filling with the plasma. Such containers shall be uncolored and hermetically sealed, and shall permit clear visibility of the contents. Final containers and their components shall not interact with the plasma contents under conditions of storage and use so as to alter the safety, quality, purity, or potency of the plasma and shall provide adequate protection against external factors that may cause deterioration or contamination. Prior to filling, the final container shall be marked or identified by number or other symbol which will relate it directly to the donor.

(c) *Preservative.* Source Plasma shall not contain a preservative.

[38 FR 32089, Nov. 20, 1973, as amended at 41 FR 10769, Mar. 12, 1976; 50 FR 4140, Jan. 29, 1985]

§ 640.69 General requirements.

(a) *Pooling.* Two units of Source Plasma from the same donor may be pooled if such units are collected during one plasmapheresis procedure: *Provided,* That the pooling is done by a procedure that does not introduce a risk of contamination of the red blood cells and, for plasma intended for injectable products, gives maximum assurance of a sterile container of plasma.

(1) The pooling of plasma from two or more donors is not permitted in the manufacture of Source Plasma intended for manufacturing into injectable products.

(2) The pooling of plasma from two or more donors by the manufacturer of Source Plasma intended for manufacturing into noninjectable products is permitted: *Provided,* That the plasma from two or more donors is pooled after the plasma has been removed from the red blood cells, and after the red blood cell containers are sealed.

(b) *Storage.* Immediately after filling, plasma intended for manufacturing into injectable products shall be stored at a temperature not warmer than −20 °C, except for plasma collected as provided in § 640.74. Plasma intended for manufacturing into noninjectable products may be stored at temperatures appropriate for the intended use of the final product, provided these temperatures are included in the Source Plasma license application.

(c) *Inspection.* Source Plasma intended for manufacturing into injectable products shall be inspected for evidence of thawing at the time of issuance, except that inspection of individual plasma containers need not be made if the records of continuous monitoring of the storage temperature establish that the temperature remained at −20 °C or colder. If there is evidence that the storage temperature has not been maintained at −20 °C or colder, the plasma may be relabeled and issued as provided in § 640.76(a).

(d) *Samples.* If samples are provided, they shall meet the following standards:

(1) Prior to filling, all samples shall be marked or identified so as to relate them directly to the donor of that unit of plasma.

(2) All samples shall be filled at the time the final product is prepared by the person who prepares the final product.

(3) All samples shall be representative of the contents of the final product or be collected from the donor at the time of filling the collection container.

(4) All samples shall be collected in a manner that does not contaminate the contents of the final container.

[38 FR 32089, Nov. 20, 1973, as amended at 41 FR 10769, Mar. 12, 1976; 41 FR 14367, Apr. 5, 1976; 50 FR 4140, Jan. 29, 1985; 63 FR 16685, Apr. 6, 1998; 64 FR 45374, Aug. 19, 1999]

§ 640.71 Manufacturing responsibility.

(a) All steps in the manufacturing of Source Plasma, including donor examination, blood collection, plasmapheresis, laboratory testing, labeling, storage, and issuing shall be performed by personnel of the establishment licensed to manufacture Source Plasma, except that the following tests may be performed by personnel of an establishment licensed for blood and blood derivatives under section 351(a) of the Public Health Service Act, or by a clinical laboratory that meets the standards of the Clinical Laboratories Improvement Amendments of 1988 (CLIA) (42 U.S.C. 263a): *Provided,* The establishment or clinical laboratory is qualified to perform the assigned test(s).

(1) The test for hepatitis B surface antigen.

(2) The total plasma or serum protein and the quantitative test for plasma or serum proteins or for immunoglobulins.

(3) The serologic test for syphilis.

(4) A test for antibody to HIV.

(b) Such testing shall not be considered divided manufacturing, which requires two biologics licenses for Source Plasma: *Provided,* That

(1) The results of such tests are maintained by the licensed manufacturer of the Source Plasma whereby such results may be reviewed by a licensed physician as required in § 640.65(b)(2) of this chapter and by an authorized representative of the Food and Drug Administration.

(2) The Source Plasma manufacturer has obtained a written agreement that the testing laboratory will permit authorized representatives of the Food and Drug Administration to inspect its testing procedures and facilities during reasonable business hours.

(3) The testing laboratory will participate in any proficiency testing programs undertaken by the Center for Biologics Evaluation and Research, Food and Drug Administration.

[41 FR 10770, Mar. 12, 1976, as amended at 49 FR 23834, June 8, 1984; 50 FR 4140, Jan. 29, 1985; 53 FR 117, Jan. 5, 1988; 55 FR 11013, Mar. 26, 1990; 64 FR 45374, Aug. 19, 1999; 64 FR 56453, Oct. 20, 1999; 66 FR 1837, Jan. 10, 2001]

§ 640.72 Records.

(a) In addition to the recordkeeping requirements of this subchapter, the following records shall be maintained:

(1) Documentation shall be available to ensure that the shipping temperature requirements of § 600.15 of this title and of § 640.74(b)(2) are being met for Source Plasma intended for manufacture into injectable products.

(2) For each donor, a separate and complete record of all initial and periodic examinations, tests, laboratory data, interviews, etc., undertaken pursuant to §§ 640.63, 640.65, 640.66, and 640.67, except that negative test results for hepatitis B surface antigen, negative test results for antibody to HIV, and the volume or weight of plasma withdrawn from a donor need not be kept on the individual donor record: *Provided,* That such information is

maintained on the premises of the plasmapheresis center where the donor's plasma has been collected.

(3) The original or a clear copy of the donor's written consent for participation in the plasmapheresis program or for immunization.

(4) The certification of the donor's good health as prescribed in § 640.63(b)(3).

(5) If plasma that is reactive to a serologic test for syphilis is issued as prescribed in § 640.65(b)(2)(iv), the distribution records shall indicate by number those units that are reactive.

(b) Each donor record must be directly cross-referenced to the unit(s) of Source Plasma associated with the donor.

(c) If a repeat donor is rejected or a donor's plasma is found unsuitable, the donor's record shall contain a full explanation for the rejection.

(d) If a donor has a reaction while on the plasmapheresis premises, or a donor reaction is reported to the center after the donor has left the premises, the donor's record shall contain a full explanation of the reaction, including the measures taken to assist the donor and the outcome of the incident.

[41 FR 10770, Mar. 12, 1976, as amended at 50 FR 4140, Jan. 29, 1985; 53 FR 117, Jan. 5, 1988; 64 FR 45374, Aug. 19, 1999; 67 FR 9587, Mar. 4, 2002]

§ 640.73 Reporting of fatal donor reactions.

If a donor has a fatal reaction which, in any way, may be associated with plasmapheresis the Director of the Center for Biologics Evaluation and Research shall be notified by telephone as soon as possible. If the facility is located outside of the continental United States, notification by cable or telegram shall be acceptable.

[41 FR 10770, Mar. 12, 1976, as amended at 49 FR 23834, June 8, 1984; 55 FR 11013, Mar. 26, 1990]

§ 640.74 Modification of Source Plasma.

(a) Upon approval by the Director, Center for Biologics Evaluation and Research, Food and Drug Administration, of a supplement to the biologics license application for Source Plasma, a manufacturer may prepare Source Plasma as a liquid product for a licensed blood derivative manufacturer who has indicated a need for a liquid product.

(b) Source Plasma Liquid shall meet all standards of the frozen Source Plasma except:

(1) Source Plasma Liquid shall be stored in nonleachable containers so that the containers and their components will not interact with the plasma contents under conditions of storage and use so as to alter the safety, quality, purity, or potency of the plasma and shall provide adequate protection against external factors that may cause deterioration or contamination.

(2) Source Plasma Liquid shall be shipped, stored and labeled for storage at a temperature of 10 °C or colder. An exception to the shipping or storage temperature shall be approved by the Director, Center for Biologics Evaluation and Research, Food and Drug Administration, based upon his receipt of substantial evidence to support another temperature. Such evidence may be submitted by either the licensed manufacturer of the Source Plasma Liquid or the manufacturer of the final blood derivative product who has requested the Source Plasma Liquid.

(3) The label for the Source Plasma Liquid shall be easily distinguished from that of the frozen product. Color coding shall not be used for this purpose.

(4) The label affixed to each container of Source Plasma Liquid shall contain, in addition to the information required by § 606.121 of this chapter, but excluding § 606.121(e)(5)(ii) of this chapter, the name of the manufacturer of the final blood derivative product for whom it was prepared.

(5) Source Plasma Liquid shall be inspected immediately prior to issuance. If the color or physical appearance is abnormal, or there is any indication or suspicion of microbial contamination, the unit of Source Plasma Liquid shall not be issued.

[38 FR 32089, Nov. 20, 1973. Redesignated and amended at 41 FR 10770, Mar. 12, 1976; 49 FR 23834, June 8, 1984; 50 FR 4140, Jan. 29, 1985; 55 FR 11013, Mar. 26, 1990; 59 FR 49351, Sept. 28, 1994; 63 FR 16685, Apr. 6, 1998; 64 FR 56454, Oct. 20, 1999; 77 FR 18, Jan. 3, 2012]

§ 640.76 Products stored or shipped at unacceptable temperatures.

(a) *Storage temperature.* (1) Except as provided in paragraph (a)(2) of this section, Source Plasma intended for manufacture into injectable products that is inadvertently exposed (i.e., an unforeseen occurrence in spite of compliance with good manufacturing practice) to a storage temperature warmer than −20 °C and colder than +10 °C may be issued only if labeled as "Source Plasma Salvaged." The label shall be revised before issuance, and appropriate records shall be maintained identifying the units involved, describing their disposition, and explaining fully the conditions that caused the inadvertent temperature exposure.

(2) Source Plasma intended for manufacture into injectable products that is exposed inadvertently (i.e., an unforeseen occurrence in spite of compliance with good manufacturing practice) to one episode of storage temperature fluctuation that is warmer than −20 °C and colder than −5 °C for not more than 72 hours is exempt from the labeling requirements of paragraph (a)(1) of this section, provided that the plasma has been and remains frozen solid. Appropriate records shall be maintained identifying the units involved, describing their disposition, explaining fully the conditions that caused the inadvertent temperature exposure, and documenting that the episode of temperature elevation did not exceed 72 hours, that the temperature did not rise to warmer than −5 °C in storage, and that the plasma remained frozen solid throughout the period of elevated temperature. When requested, copies of the records shall be provided to the plasma derivative manufacturer.

(b) *Shipping temperature.* If Source Plasma for manufacture into injectable products is exposed inadvertently (i.e., an unforeseen occurrence in spite of compliance with good manufacturing practice) to a shipping temperature warmer than −5 °C and colder than +10 °C, the plasma derivative manufacturer shall label it "Source Plasma Salvaged." Appropriate records shall be maintained identifying the units involved, describing their disposition, and explaining fully the conditions that caused the inadvertent temperature exposure.

(c) *Relabeling.* If Source Plasma is required to be relabeled as "Source Plasma Salvaged" under paragraph (a)(1) or (b) of this section, the person responsible for the relabeling shall cover the original label with either (1) a complete new label containing the appropriate information or (2) a partial label affixed to the original label and containing the appropriate new information, which covers the incorrect information regarding storage temperature.

[45 FR 80501, Dec. 5, 1980, as amended at 50 FR 4140, Jan. 29, 1985]

Subpart H—Albumin (Human)

§ 640.80 Albumin (Human).

(a) *Proper name and definition.* The proper name of the product shall be Albumin (Human). The product is defined as a sterile solution of the albumin derived from human plasma.

(b) *Source material.* The source material of Albumin (Human) shall be plasma recovered from Whole Blood prepared as prescribed in §§ 640.1 through 640.5, or Source Plasma prepared as prescribed in §§ 640.60 through 640.76.

(c) *Additives in source material.* Source material shall not contain an additive unless it is shown that the processing method yields a final product free of the additive to such extent that the continued safety, purity, potency, and effectiveness of the final product will not be adversely affected.

[42 FR 27582, May 31, 1977, as amended at 50 FR 4140, Jan. 29, 1985; 64 FR 26286, May 14, 1999]

§ 640.81 Processing.

(a) *Date of manufacture.* The date of manufacture shall be the date of final sterile filtration of a uniform pool of bulk solution.

(b) *Processing method.* The processing method shall not affect the integrity of the product, and shall have been shown to yield consistently a product which is safe for intravenous injection.

(c) *Microbial contamination.* All processing steps shall be conducted in a manner to minimize the risk of contamination from microorganisms,

pyrogens, or other impurities. Preservatives to inhibit growth of microorganisms shall not be used during processing.

(d) *Storage of bulk fraction.* Bulk concentrate to be held more than 1 week prior to further processing shall be stored in clearly identified closed vessels at a temperature of −5 °C or colder. Any other bulk form of the product, exclusive of the sterile bulk solution, to be held more than 1 week prior to further processing shall be stored in clearly identified closed vessels at a temperature of 5 °C or colder. Any bulk fraction to be held one week or less prior to further processing shall be stored in clearly identified closed vessels at a temperature of 5 °C or colder.

(e) *Heat treatment.* Heating of the final containers of Albumin (Human) shall begin within 24 hours after completion of filling. Heat treatment shall be conducted so that the solution is heated continuously for not less than 10, or more than 11 hours, at an attained temperature of 60±0.5 °C.

(f) *Stabilizer.* Either 0.08±0.016 millimole sodium caprylate, or 0.08±0.016 millimole sodium acetyltryptophanate and 0.08±0.016 millimole sodium caprylate per gram of protein shall be present as a stabilizer(s). Calculations of the stabilizer concentration may employ the labeled value for the protein concentration of the product as referred to in § 640.84(d).

(g) *Incubation.* All final containers of Albumin (Human) shall be incubated at 20 to 35 °C for at least 14 days following the heat treatment prescribed in paragraph (e) of this section. At the end of this incubation period, each final container shall be examined and all containers showing any indication of turbidity or microbial contamination shall not be issued. The contents of turbid final containers shall be examined microscopically and tested for sterility. If growth occurs, organisms shall be identified as to genus, and the material from such containers shall not be used for further manufacturing.

[42 FR 27582, May 31, 1977, as amended at 50 FR 4140, Jan. 29, 1985; 64 FR 26286, May 14, 1999; 65 FR 13679, Mar. 14, 2000; 65 FR 52018, Aug. 28, 2000]

§ 640.82 Tests on final product.

Tests shall be performed on the final product to determine that it meets the following standards:

(a) *Protein concentration.* Final product shall conform to one of the following concentrations: 4.0 ±0.25 percent; 5.0 ±0.30 percent; 20.0 ±1.2 percent; and 25.0 ±1.5 percent solution of protein.

(b) *Protein composition.* At least 96 percent of the total protein in the final product shall be albumin, as determined by a method that has been approved for each manufacturer by the Director, Center for Biologics Evaluation and Research, Food and Drug Administration.

(c) *pH.* The pH shall be 6.9 ±0.5 when measured in a solution of the final product diluted to a concentration of 1 percent protein with 0.15 molar sodium chloride.

(d) *Sodium concentration.* The sodium concentration of the final product shall be 130 to 160 milliequivalents per liter.

(e) *Potassium concentration.* The potassium concentration of the final product shall not exceed 2 milliequivalents per liter.

(f) *Heat stability.* A final container sample of Albumin (Human) shall remain unchanged, as determined by visual inspection, after heating at 57 °C for 50 hours, when compared to its control consisting of a sample, from the same lot, which has not undergone this heating.

[42 FR 27582, May 31, 1977, as amended at 49 FR 23834, June 8, 1984; 50 FR 4140, Jan. 29, 1985; 55 FR 11013, Mar. 26, 1990; 64 FR 26286, May 14, 1999]

§ 640.83 General requirements.

(a) *Preservative.* The final product shall not contain a preservative.

(b) *Storage of bulk solution.* After all processing steps have been completed, the sterile bulk solution shall be stored in a manner that will ensure the continued sterility of the product, and at a temperature that shall not exceed the recommended storage temperature of the final product prescribed in § 610.53 of this chapter.

[42 FR 27582, May 31, 1977]

§ 640.84 Labeling.

In addition to the labeling requirements of §§ 610.60, 610.61, and 610.62 of this chapter, the container and package labels shall contain the following information:

(a) The osmotic equivalent in terms of plasma, and the sodium concentration in terms of a value or a range in milliequivalents per liter;

(b) The cautionary statement placed in a prominent position on the label, "Do Not Use if Turbid. Do Not Begin Administration More Than 4 Hours After the Container Has Been Entered.";

(c) The need for additional fluids when 20 percent or 25 percent albumin is administered to a patient with marked dehydration;

(d) The protein concentration, expressed as a 4 percent, 5 percent, 20 percent, or 25 percent solution.

[42 FR 27582, May 31, 1977, as amended at 49 FR 2244, Jan. 19, 1984; 64 FR 26286, May 14, 1999]

Subpart I—Plasma Protein Fraction (Human)

SOURCE: 42 FR 27583, May 31, 1977, unless otherwise noted.

§ 640.90 Plasma Protein Fraction (Human).

(a) *Proper name and definition.* The proper name of the product shall be Plasma Protein Fraction (Human). The product is defined as a sterile solution of protein composed of albumin and globulin, derived from human plasma.

(b) *Source material.* The source material of Plasma Protein Fraction (Human) shall be plasma recovered from Whole Blood prepared as prescribed in §§ 640.1 through 640.5, or Source Plasma prepared as prescribed in §§ 640.60 through 640.76.

(c) *Additives in source material.* Source material shall not contain an additive unless it is shown that the processing method yields a final product free of the additive to such extent that the continued safety, purity, potency, and effectiveness of the final product will not be adversely affected.

[42 FR 27583, May 31, 1977, as amended at 64 FR 26286, May 14, 1999]

§ 640.91 Processing.

(a) *Date of manufacture.* The date of manufacture shall be the date of final sterile filtration of a uniform pool of bulk solution.

(b) *Processing method.* The processing method shall not affect the integrity of the product, and shall have been shown to yield consistently a product which:

(1) After the heating prescribed in paragraph (e) of this section does not show an increase in the components with electrophoretic mobility similar to that of alpha globulin that amounts to more than 5 percent of the total protein.

(2) Contains less than 5 percent protein with a sedimentation coefficient greater than 7.0 S.

(3) Is safe for intravenous injection.

(c) *Microbial contamination.* All processing steps shall be conducted in a manner to minimize the risk of contamination from microorganisms, pyrogens, or other impurities. Preservatives to inhibit growth of microorganisms shall not be used during processing.

(d) *Storage of bulk fraction.* Bulk concentrate to be held more than 1 week prior to further processing shall be stored in clearly identified closed vessels at a temperature of −5 °C or colder. Any other bulk form of the product (exclusive of the sterile bulk solution) to be held more than 1 week prior to further processing, shall be stored in clearly identified closed vessels at a temperature of 5 °C or colder. Any bulk fraction to be held one week or less prior to further processing shall be stored in clearly identified closed vessels at a temperature of 5 °C or colder.

(e) *Heat treatment.* Heating of the final containers of Plasma Protein Fraction (Human) shall begin within 24 hours after completion of filling. Heat treatment shall be conducted so that the solution is heated continuously for not less than 10 or more than 11 hours at an attained temperature of 60±0.5 °C.

(f) *Stabilizer.* Either 0.08±0.016 millimole sodium caprylate, or 0.08±0.016 millimole sodium acetyltryptophanate and 0.08±0.016 millimole sodium caprylate per gram of protein shall be present as a stabilizer(s). Calculations of the stabilizer concentration may employ the labeled

value 5 percent for the protein concentration of the product.

(g) *Incubation.* All final containers of Plasma Protein Fraction (Human) shall be incubated at 20 to 35 °C for at least 14 days following the heat treatment prescribed in paragraph (e) of this section. At the end of this incubation period, each final container shall be examined and all containers showing any indication of turbidity or microbial contamination shall not be issued. The contents of turbid final containers shall be examined microscopically and tested for sterility. If growth occurs, the types of organisms shall be identified as to genus and the material from such containers shall not be used for further manufacturing.

[42 FR 27583, May 31, 1977, as amended at 64 FR 26286, May 14, 1999]

§ 640.92 Tests on final product.

Tests shall be performed on the final product to determine that it meets the following standards:

(a) *Protein concentration.* The final product shall be a 5.0 ±0.30 percent solution of protein.

(b) *Protein composition.* The total protein in the final product shall consist of at least 83 percent albumin, and no more than 17 percent globulins. No more than 1 percent of the total protein shall be gamma globulin. The protein composition shall be determined by a method that has been approved for each manufacturer by the Director, Center for Biologics Evaluation and Research, Food and Drug Administration.

(c) *pH.* The pH shall be 7.0 ±0.3 when measured in a solution of the final product diluted to a concentration of 1 percent protein with 0.15 molar sodium chloride.

(d) *Sodium concentration.* The sodium concentration of the final product shall be 130 to 160 milliequivalents per liter.

(e) *Potassium concentration.* The potassium concentration of the final product shall not exceed 2 milliequivalents per liter.

(f) *Heat stability.* A final container sample of Plasma Protein Fraction (Human) shall remain unchanged, as determined by visual inspection, after heating at 57 °C for 50 hours, when compared to its control consisting of a sample, from the same lot, which has not undergone this heating.

[42 FR 27583, May 31, 1977, as amended at 49 FR 23834, June 8, 1984; 55 FR 11013, Mar. 26, 1990; 64 FR 26286, May 14, 1999; 65 FR 13679, Mar. 14, 2000]

§ 640.93 General requirements.

(a) *Preservative.* The final product shall not contain a preservative.

(b) *Storage of bulk solution.* After all processing steps have been completed, the sterile bulk solution shall be stored in a manner that will ensure the continued sterility of the product, and at a temperature that shall not exceed the recommended storage temperature of the final product prescribed in § 610.53 of this chapter.

§ 640.94 Labeling.

In addition to the labeling requirements of §§ 610.60, 610.61, and 610.62 of this chapter, the container and package labels shall contain the following information:

(a) The osmotic equivalent in terms of plasma, and the sodium concentration in terms of a value or a range in milliequivalents per liter.

(b) The cautionary statement placed in a prominent position on the label, "Do Not Use if Turbid. Do Not Begin Administration More than 4 Hours After the Container Has Been Entered."

[42 FR 27583, May 31, 1977, as amended at 49 FR 2244, Jan. 19, 1984; 64 FR 26286, May 14, 1999]

Subpart J—Immune Globulin (Human)

§ 640.100 Immune Globulin (Human).

(a) *Proper name and definition.* The proper name of this product shall be Immune Globulin (Human). The product is defined as a sterile solution containing antibodies derived from human plasma.

(b) *Source material.* The source material of Immune Globulin (Human) shall be plasma recovered from Whole Blood prepared as prescribed in §§ 640.1 through 640.5, or Source Plasma prepared as prescribed in §§ 640.60 through 640.76.

(c) *Additives in source material.* The source material shall contain no additives other than citrate or acid citrate dextrose anticoagulant solution, unless it is shown that the processing method yields a product free of the additive to such an extent that the safety, purity, and potency of the product will not be affected adversely.

[38 FR 32089, Nov. 20, 1973, as amended at 50 FR 4140, Jan. 29, 1985; 64 FR 26287, May 14, 1999]

§ 640.101 General requirements.

(a) *Heat stability test.* Approximately 2 ml. of completely processed material of each lot shall not show any visible sign of gelation after heating in a 12×75 mm. stoppered glass tube at 57 °C for 4 hours.

(b) *pH.* The pH of final container material shall be 6.8 ±0.4 when measured in a solution diluted to 1 percent protein with 0.15 molar sodium chloride.

(c) *Turbidity.* The product shall be free of turbidity as determined by visual inspection of final containers.

(d) *Date of manufacture.* The date of manufacture is the date of initiating the last valid measles or poliomyelitis antibody test (§ 640.104(b) (2) and (3)) whichever date is earlier.

(e) *Labeling.* In addition to complying with all applicable labeling required in this subchapter, labeling shall indicate that:

(1) There is no prescribed potency for viral hepatitis antibodies.

(2) The product is not recommended for intravenous administration.

[38 FR 32089, Nov. 20, 1973; 48 FR 13026, Mar. 29, 1983, as amended at 49 FR 23834, June 8, 1984; 50 FR 4140, Jan. 29, 1985; 51 FR 15611, Apr. 25, 1986; 55 FR 11013, Mar. 26, 1990; 63 FR 16685, Apr. 6, 1998; 64 FR 26287, May 14, 1999]

§ 640.102 Manufacture of Immune Globulin (Human).

(a) *Processing method.* The processing method shall be one that has been shown: (1) To be capable of concentrating tenfold from source material at least two different antibodies; (2) not to affect the integrity of the globulins; (3) to consistently yield a product which is safe for subcutaneous and intramuscular injection and (4) not to transmit viral hepatitis.

(b) *Microbial contamination.* Low temperatures or aseptic techniques shall be used to minimize contamination by microorganisms. Preservatives to inhibit growth of microorganisms shall not be used during processing.

(c) *Bulk storage.* The globulin fraction may be stored in bulk prior to further processing provided it is stored in clearly identified hermetically closed vessels. Globulin as either a liquid concentrate or a solid and containing alcohol or more than 5 percent moisture shall be stored at a temperature of −10 °C or lower. Globulin as a solid free from alcohol and containing less than 5 percent moisture, shall be stored at a temperature of 0 °C or lower.

(d) *Determination of the lot.* Each lot of Immune Globulin (Human) shall represent a pooling of approximately equal amounts of material from not less than 1,000 donors.

(e) *Sterilization and heating.* The final product shall be sterilized promptly after solution. At no time during processing shall the product be exposed to temperatures above 45 °C, and after sterilization the product shall not be exposed to temperatures above 32 °C for more than 72 hours.

[38 FR 32089, Nov. 20, 1973, as amended at 50 FR 4140, Jan. 29, 1985; 63 FR 16685, Apr. 6, 1998; 64 FR 26287, May 14, 1999; 65 FR 13679, Mar. 14, 2000; 65 FR 52018, Aug. 28, 2000]

§ 640.103 The final product.

(a) *Final solution.* The final product shall be a 16.5 ±1.5 percent solution of globulin containing 0.3 molar glycine and a preservative.

(b) *Protein composition.* At least 96 percent of the total protein shall be immunoglobulin G (IgG), as determined by a method that has been approved for each manufacturer by the Director, Center for Biologics Evaluation and Research, Food and Drug Administration.

[38 FR 32089, Nov. 20, 1973, as amended at 64 FR 26287, May 14, 1999]

§ 640.104 Potency.

(a) *Antibody levels and tests.* Each lot of final product shall contain at least the minimum levels of antibodies for diphtheria, measles, and for at least one type of poliomyelitis. In the event the final bulk solution is stored at a

temperature above 5 °C the antibody level tests shall be performed after such storage with a sample of the stored material.

(b) *Minimum levels.* The minimum antibody levels are as follows:

(1) No less than 2 units of diphtheria antitoxin per ml.

(2) A measles neutralizing antibody level that, when compared with that of a reference material designated by the Center for Biologics Evaluation and Research (CBER), Food and Drug Administration, as indicated in paragraph (c) of this section, demonstrates adequate potency. The Director, CBER, shall notify manufacturers when a new reference material will be used and will advise manufacturers of an appropriate antibody level taking into account a comparison of the new reference material to the previous reference material.

(3) A poliomyelitis Type 1, Type 2, or Type 3 neutralizing antibody level that, when compared with that of a reference material designated by the Center for Biologics Evaluation and Research, Food and Drug Administration, as indicated in paragraph (c) of this section, demonstrates adequate potency. The Director, CBER, shall notify manufacturers when a new reference material will be used and will advise manufacturers of an appropriate antibody level taking into account a comparison of the new reference material to the previous reference material.

(c) *Reference materials.* The following reference materials shall be obtained from the Center for Biologics Evaluation and Research:

(1) Reference Immune Globulin for correlation of measles antibody titers.

(2) Reference Immune Globulin for correlation of poliomyelitis antibody titers, Types 1, 2, and 3.

[38 FR 32069, Nov. 20, 1973, as amended at 39 FR 9661, Mar. 13, 1974; 49 FR 23834, June 8, 1984; 50 FR 4140, Jan. 29, 1985; 55 FR 11013, Mar. 26, 1990; 63 FR 16685, Apr. 6, 1998; 64 FR 26287, May 14, 1999]

Subpart K [Reserved]

Subpart L—Alternative Procedures

§ 640.120 Alternative procedures.

(a) The Director, Center for Biologics Evaluation and Research, may approve an exception or alternative to any requirement in subchapter F of chapter I of title 21 of the Code of Federal Regulations regarding blood, blood components, or blood products. Requests for such exceptions or alternatives shall ordinarily be in writing. Licensed establishments shall submit such requests in accordance with § 601.12 of this chapter. However, in limited circumstances, such requests may be made orally and permission may be given orally by the Director. Oral requests and approvals must be promptly followed by written requests and written approvals.

(b) FDA will publish a list of approved alternative procedures and exceptions periodically in the FEDERAL REGISTER.

[55 FR 10423, Mar. 21, 1990, as amended at 62 FR 39903, July 24, 1997]

PART 660—ADDITIONAL STANDARDS FOR DIAGNOSTIC SUBSTANCES FOR LABORATORY TESTS

Subpart A—Antibody to Hepatitis B Surface Antigen

Sec.

Subpart B [Reserved]

Subpart C—Blood Grouping Reagent

Subpart D—Reagent Red Blood Cells