SUBCHAPTER F—BIOLOGICS

PART 600—BIOLOGICAL PRODUCTS: GENERAL

Subpart A—General Provisions

Sec. 600.3 Definitions.

Subpart B—Establishment Standards

600.10 Personnel.
600.11 Physical establishment, equipment, animals, and care.
600.12 Records.
600.13 Retention samples.
600.14 Reporting of biological product deviations by license manufacturers.
600.15 Temperatures during shipment.

Subpart C—Establishment Inspection

600.20 Inspectors.
600.21 Time of inspection.
600.22 Duties of inspector.

Subpart D—Reporting of Adverse Experiences

600.80 Postmarketing reporting of adverse experiences.
600.81 Distribution reports.
600.90 Waivers.


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

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

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

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

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

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

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

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

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

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

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

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

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

(s) The word potency is interpreted to mean the specific ability or capacity of the product, as indicated by appropriate laboratory tests or by adequately controlled clinical data obtained through the administration of the product in the manner intended, to effect a given result.

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

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

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

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

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

(y) A filling refers to a group of final containers identical in all respects, which have been filled with the same product from the same bulk lot without any change that will affect the integrity of the filling assembly.
(z) Process refers to a manufacturing step that is performed on the product itself which may affect its safety, purity or potency, in contrast to such manufacturing steps which do not affect intrinsically the safety, purity or potency of the product.

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

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

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

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

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

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

(gg) Supplement is a request to the Director, Center for Biologics Evaluation and Research, to approve a change in an approved license application.

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

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

§ 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-bearing pathogenic microorganisms are not involved and provided the space is thoroughly cleaned and disinfected before the manufacture of products is resumed.

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

(3) Work with spore-bearing organisms. Except as provided in the previous paragraph, all work with spore-bearing microorganisms shall be done in an entirely separate building: Provided, That such work may be done in a portion of a building used in the manufacture of products not containing spore-bearing microorganisms if such portion is completely walled-off and is constructed so as to prevent contamination of other areas and if entrances to such portion are independent of the remainder of the building. All vessels, apparatus and equipment used for spore-bearing microorganisms shall be permanently identified and reserved exclusively for use with those organisms. Materials destined for further manufacturing may be removed from such an area only under conditions which will prevent the introduction of spores into other manufacturing areas.

(4) Live vaccine processing. Space used for processing a live vaccine shall not be used for any other purpose during the processing period for that vaccine and such space shall be decontaminated prior to initiation of the processing. Live vaccine processing areas shall be isolated from and independent of any space used for any other purpose by being either in a separate building, in a separate wing of a building, or in quarters at the blind end of a corridor and shall include adequate space and equipment for all processing steps up to filling into final containers. Test procedures which potentially involve the presence of microorganisms other than the vaccine strains, or the use of tissue culture cell lines other than primary cultures, shall not be conducted in space used for processing live vaccine.

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

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

(2) Quarantine of animals—(i) General. No animal shall be used in processing unless kept under competent daily inspection and preliminary quarantine for a period of at least 7 days before use, or as otherwise provided in this subchapter. Only healthy animals free from detectable communicable diseases shall be used. Animals must remain in overt good health throughout the quarantine periods and particular care shall be taken during the quarantine periods to reject animals of the equine genus which may be infected with glanders and animals which may be infected with tuberculosis.

(ii) Quarantine of monkeys. In addition to observing the pertinent general quarantine requirements, monkeys used as a source of tissue in the manufacture of vaccine shall be maintained in quarantine for at least 6 weeks prior to use, except when otherwise provided in this part. Only 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.

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

(h) Containers and closures. All final containers and closures shall be made of material that will not hasten the deterioration of the product or otherwise render it less suitable for the intended use. All final containers and closures shall be clean and free of surface solids, leachable contaminants and other materials that will hasten the deterioration of the product or otherwise render it less suitable for the intended use. After filling, sealing shall be performed in a manner that will maintain the integrity of the product during the dating period. In addition, final containers and closures for products intended for use by injection shall be sterile and free from pyrogens. Except as otherwise provided in the regulations of this subchapter, final containers for products intended for use by injection shall be colorless and sufficiently transparent to permit visual examination of the contents under normal light. As soon as possible after filling final containers shall be labeled as prescribed in §610.60 et seq. of this chapter, except
that final containers may be stored without such prescribed labeling provided they are stored in a sealed receptacle labeled both inside and outside with at least the name of the product, the lot number, and the filling identification.


§ 600.12 Records.

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

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

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

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

Provided, That a summary of such records shall be retained.

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

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

(e) Records in case of divided manufacturing responsibility. If two or more establishments participate in the manufacture of a product, the records of each such establishment must show plainly the degree of its responsibility. In addition, each participating manufacturer shall furnish to the manufacturer who prepares the product in final form for sale, barter or exchange, a copy of all records relating to the manufacturing operations performed by such participating manufacturer insofar as they concern the safety, purity and potency of the lots of the product involved, and the manufacturer who prepares the product in final form shall retain a complete record of all the manufacturing operations relating to the product.


§ 600.13 Retention samples.

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


§ 600.14 Reporting of biological product deviations by licensed manufacturers.

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

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

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

(iii) Persons who manufacture Source Plasma or any other blood component and use that Source Plasma or any other blood component in the further manufacture of another licensed biological product must report:
(A) Under §606.171 of this chapter, if a biological product deviation occurs during the manufacture of that Source Plasma or any other blood component; or
(B) Under this section, if a biological product deviation occurs after the manufacture of that Source Plasma or any other blood component, and during manufacture of the licensed biological product.

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

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

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

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

(3) Involves a distributed biological product.

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

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

(e) Where do I report under this section? You must send the completed
Food and Drug Administration, HHS

Form FDA–3486 to the Director, Office of Compliance and Biologics Quality (HFM–600), Center for Biologics Evaluation and Research, 1401 Rockville Pike, suite 200N, Rockville, MD 20852–1448, by either a paper or an electronic filing:

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

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

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

[65 FR 66634, Nov. 7, 2000]

§ 600.15 Temperatures during shipment.

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

(a) Products.

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

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


Subpart C—Establishment Inspection

§ 600.20 Inspectors.

Inspections shall be made by an officer of the Food and Drug Administration having special knowledge of the
§ 600.21 Time of inspection.

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

§ 600.22 Duties of inspector.

The inspector shall:

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

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

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

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

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

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

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

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

§ 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...
(b) Review of adverse experiences. Any person having a biologics license under §601.20 of this chapter shall promptly review all adverse experience information pertaining to its product obtained or otherwise received by the licensed manufacturer from any source, foreign or domestic, including information derived from commercial marketing experience, postmarketing clinical investigations, postmarketing epidemiological/surveillance studies, reports in the scientific literature, and unpublished scientific papers. Licensed manufacturers are not required to resubmit to FDA adverse product experience reports forwarded to the licensed manufacturer by FDA; licensed manufacturers, however, must submit all followup information on such reports to FDA. Any person subject to the reporting requirements under paragraph (c) of this section shall also develop written procedures for the surveillance, receipt, evaluation, and reporting of postmarketing adverse experiences to FDA.

(c) Reporting requirements. The licensed manufacturer shall report to FDA adverse experience information, as described in this section. The licensed manufacturer shall submit two copies of each report described in this section for nonvaccine biological products, to the Center for Biologics Evaluation and Research (HFM–210), Food and Drug Administration, 1401 Rockville Pike, suite 200 N., Rockville, MD 20852–1448. Submit all vaccine adverse experience reports to: Vaccine Adverse Event Reporting System (VAERS), P.O. Box 1100, Rockville, MD 20849–1100. FDA may waive the requirement for the second copy in appropriate instances.

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

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

(iii) Submission of reports. The requirements of paragraphs (c)(1)(i) and (c)(1)(ii) of this section, concerning the submission of postmarketing 15-day Alert reports, shall also apply to any person whose name appears on the label of a licensed biological product as a manufacturer, packer, distributor, shared manufacturer, joint manufacturer, or any other participant involved in divided manufacturing. To avoid unnecessary duplication in the submission to FDA of reports required by paragraphs (c)(1)(i) and (c)(1)(ii) of this section, obligations of persons other than the licensed manufacturer of the final 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 these circumstances, 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 re-establish 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 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.

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

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

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

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

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

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

(4) Copies of the reporting form designated by FDA (FDA–3500A) for nonvaccine biological products may be obtained from the Center for Biologics Evaluation and Research (address above). Additional supplies of the form may be obtained from the Consolidated Forms and Publications Distribution Center, 3222 Hubbard Rd., Landover, MD 20785. Supplies of the VAERS form may be obtained from VAERS by calling 1–800–822–7967.

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

(h) Patient privacy. For nonvaccine biological products, a licensed manufacturer should not include in reports under this section the names and addresses of individual patients; instead, the licensed manufacturer should assign a unique code number to each report, preferably not more than eight characters in length. The licensed manufacturer should include the name of the reporter from whom the information was received. The names of patients, health care professionals, hospitals, and geographical identifiers in
§ 600.81 Distribution reports.

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

§ 600.90 Waivers.

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

(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.

PART 601—LICENSING

Subpart A—General Provisions

Sec.
601.2 Applications for biologics licenses; procedures for filing.
601.4 Issuance and denial of license.
601.5 Revocation of license.
601.6 Suspension of license.
601.7 Procedure for hearings.
601.8 Publication of revocation.
601.9 Licenses; reissuance.

Subpart B (Reserved)

Subpart C—Biologics Licensing

601.12 Changes to an approved application.
601.15 Foreign establishments and products: Samples for each importation.
601.20 Biologics licenses; issuance and conditions.
601.21 Products under development.
601.22 Products in short supply; initial manufacturing at other than licensed location.
601.25 Review procedures to determine that licensed biological products are safe, effective, and not misbranded under prescribed, recommended, or suggested conditions of use.
601.26 Reclassification procedures to determine that licensed biological products are safe, effective, and not misbranded under prescribed, recommended, or suggested conditions of use.
601.27 Pediatric studies.
601.28 Annual reports of postmarketing pediatric studies.
601.29 Guidance documents.

Subpart D—Diagnostic Radiopharmaceuticals

601.30 Scope.
601.31 Definition.
601.32 General factors relevant to safety and effectiveness.
601.33 Indications.
601.34 Evaluation of effectiveness.
601.35 Evaluation of safety.

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

601.40 Scope.
601.41 Approval based on a surrogate endpoint or on an effect on a clinical endpoint other than survival or irreversible morbidity.
601.42 Approval with restrictions to assure safe use.
601.43 Withdrawal procedures.
601.44 Postmarketing safety reporting.
601.45 Promotional materials.
601.46 Termination of requirements.

Subpart F—Confidentiality of Information

601.50 Confidentiality of data and information in an investigational new drug notice for a biological product.
601.51 Confidentiality of data and information in applications for biologics licenses.

Subpart G—Postmarketing Studies

601.70 Annual progress reports of postmarketing studies.

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

601.90 Scope.
601.91 Approval based on evidence of effectiveness from studies in animals.
601.92 Withdrawal procedures.
601.93 Postmarketing safety reporting.
601.94 Promotional materials.
601.95 Termination of requirements.


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, 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, if not subject to such requirements in accordance with § 56.104 or § 56.105, and was conducted in compliance with requirements for informed consent set forth in part 50 of this chapter; a full description of manufacturing methods; data establishing stability of the product through the dating period; sample(s) representative of the product for introduction or delivery for introduction into interstate commerce; summaries of results of tests performed on the lot(s) represented by the submitted sample(s); specimens of the labels, enclosures, and containers, and if applicable, any Medication Guide required under part 208 of this chapter proposed to be used for the product; and the address of each location involved in the manufacture of the biological product shall be listed in the biologics license application. The applicant shall also include a financial certification or disclosure statement(s) or both for clinical investigators as required by part 54 of this chapter. An application for a biologics license shall not be considered as filed until all pertinent information and data have been received from the manufacturer by the Center for Biologics Evaluation and Research. The applicant shall also include either a claim for categorical exclusion under § 25.30 or § 25.31 of this chapter or an environmental assessment under § 25.40 of this chapter. In lieu of the procedures described in this paragraph, applications for radioactive biological products shall be handled as set forth in paragraph (b) of this section. The applicant, or the applicant’s attorney, agent, or other authorized official shall sign the application. An application for any of the following specified categories of biological products subject to licensure shall be handled as set forth in paragraph (c) of this section:

(1) Therapeutic DNA plasmid products;
(2) Therapeutic synthetic peptide products of 40 or fewer amino acids;
(3) Monoclonal antibody products for in vivo use; and
(4) Therapeutic recombinant DNA-derived products.

(b) Radioactive biological products. To obtain marketing approval for a radioactive biological product, as defined in § 600.3(ee) of this chapter, the manufacturer of such product shall comply with the following:

(1) An applicant for a radioactive coupled antibody, which means a product that consists of an antibody component coupled with a radionuclide component (or an antibody component intended solely to be coupled with a radionuclide) in which both components provide a pharmacological effect but the biological component determines the site of action, shall submit a biologics license application to the Director, Center for Biologics Evaluation and Research, Food and Drug Administration, except if, as determined by FDA, there are significant scientific issues associated with the radionuclide or other chemically synthesized component, in which case a new drug application shall be submitted to the Center for Drug Evaluation and Research, Food and Drug Administration;

(2) An applicant for a radioactive biological product other than as described
Food and Drug Administration, HHS

§ 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 section.

[64 FR 56450, Oct. 20, 1999]

§ 601.4 Issuance and denial of license.

(a) A biologics license shall be issued upon a determination by the Director, Center for Biologics Evaluation and Research that the establishment(s) and the product meet the applicable requirements established in this chapter. A biologics license shall be valid until suspended or revoked.

(b) If the Commissioner determines that the establishment or product does not meet the requirements established in this chapter, the biologics license application shall be denied and the applicant shall be informed of the grounds for, and of an opportunity for a hearing on, the decision. If the applicant so requests, the Commissioner shall issue a notice of opportunity for hearing on the matter pursuant to §12.21(b) of this chapter.

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 Director, Center for Biologics Evaluation and Research, complete records of such deliveries and notice of suspension.

(b) Upon suspension of a license, the Commissioner shall either:

(1) Proceed under the provisions of §601.6(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]

§ 601.7 Procedure for hearings.

(a) A notice of opportunity for hearing, notice of appearance and request for hearing, and grant or denial of hearing for a biological drug pursuant to this part, for which the exemption from the Federal Food, Drug, and Cosmetic Act in §310.4 of this chapter has been revoked, shall be subject to the provisions of §314.200 of this chapter except to the extent that the notice of opportunity for hearing on the matter issued pursuant to §12.21(b) of this chapter specifically provides otherwise.

(b) Hearings pursuant to §§601.4 through 601.6 shall be governed by part 12 of this chapter.

(c) When a license has been suspended pursuant to §601.6 and a hearing request has been granted, the hearing shall proceed on an expedited basis.


§ 601.8 Publication of revocation.

Notice of revocation of a license, with statement of the cause therefor, shall be issued by the Commissioner and published in the Federal Register.

[42 FR 4718, Jan. 25, 1977]

§ 601.9 Licenses; reissuance.

(a) Compliance with requirements. A biologics license, previously suspended or revoked, may be reissued or reinstated upon a showing of compliance with requirements and upon such inspection and examination as may be considered necessary by the Director, Center for Biologics Evaluation and Research.

(b) Exclusion of noncomplying location. A biologics license, excluding a location or locations that fail to comply with the requirements in this chapter, may be issued without further application and concurrently with the suspension or revocation of the license for noncompliance at the excluded location or locations.

(c) Exclusion of noncomplying product(s). In the case of multiple products
Food and Drug Administration, HHS

§ 601.12 Changes to an approved application.

(a) General. As provided by this section, an applicant shall inform Food and Drug Administration (FDA) about each change in the product, production process, quality controls, equipment, facilities, responsible personnel, or labeling, established in the approved license application(s). Before distributing a product made using a change, an applicant shall demonstrate through appropriate validation and/or other clinical and/or non-clinical laboratory studies, the lack of adverse effect of the change on the identity, strength, quality, purity, or potency of the product as they may relate to the safety or effectiveness of the product.

(b) Changes requiring supplement submission and approval prior to distribution of the product made using the change (major changes). (1) A supplement shall be submitted for any change in the product, production process, quality controls, equipment, facilities, or responsible personnel that has 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) Changes in the qualitative or quantitative formulation or other specifications as provided in the approved application or in the regulations;

(ii) Changes requiring completion of an appropriate human study to demonstrate the equivalence of the identity, strength, quality, purity, or potency of the product as they may relate to the safety or effectiveness of the product;

(iii) Changes in the virus or adventitious agent removal or inactivation method(s);

(iv) Changes in the source material or cell line;

(v) Establishment of a new master cell bank or seed; and

(vi) Changes which may affect product sterility assurance, such as changes in product or component sterilization method(s), or an addition, deletion, or substitution of steps in an aseptic processing operation.

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

(i) A detailed description of the proposed change;

(ii) The product(s) involved;

(iii) The manufacturing site(s) or area(s) affected;

(iv) A description of the methods used and studies performed to evaluate the effect of the change on the identity, strength, quality, purity, or potency of the product as they may relate to the safety or effectiveness of the product;

(v) The data derived from such studies;

(vi) Relevant validation protocols and data; and

(vii) A reference list of relevant standard operating procedures (SOP’s).

(c) Changes requiring supplement submission at least 30 days prior to distribution of the product made using the change. (1) A supplement shall be submitted for any change in the product, production process, quality controls, equipment, facilities, or responsible personnel that has a moderate potential to have an adverse effect on the identity, strength, quality, purity, or potency of the product as they may relate to the safety or effectiveness of the product. The supplement shall be labeled “Supplement—Changes Being Effected in 30 Days” or, if applicable under paragraph (c)(5) of this section, “Supplement—Changes Being Effected.”
§ 601.12 21 CFR Ch. I (4-1-03 Edition)

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

(i) Change in the site of testing from one facility to another;

(ii) An increase or decrease in production scale during finishing steps that involves new or different equipment; and

(iii) Replacement of equipment with that of similar, but not identical, design and operating principle that does not affect the process methodology or process operating parameters.

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.

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.

(d) Changes to be described in an annual report (minor changes). (1) Changes in the product, production process, quality controls, equipment, facilities, or responsible personnel that have a minimal potential to have an adverse effect on the identity, strength, quality, purity, or potency of the product as they may relate to the safety or effectiveness of the product shall be documented by the applicant in an annual report submitted each year within 60 days of the anniversary date of approval of the application. The Director, Center for Biologics Evaluation and Research, may approve a written request for an alternative date to combine annual reports for multiple approved applications into a single annual report submission.

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

(i) Any change made to comply with an official compendium that is consistent with FDA requirements;

(ii) The deletion of an ingredient intended only to affect the color of the product except that a change intended only to affect Blood Grouping Reagents requires supplement submission and approval prior to distribution of the product made using the change in accordance with the requirements set forth in paragraph (b) of this section;

(iii) An extension of an expiration date based upon full shelf-life data obtained from a protocol approved in the application;

(iv) A change in the size of a container for a solid dosage form, without a change from one container and closure system to another;

(vi) The addition by embossing, debossing, or engraving of a code imprint to a solid dosage form biological product other than a modified release dosage form, or a minor change in an existing code imprint; and

(vii) The addition or deletion of an alternate analytical method.

The following information for each change shall be contained in the annual report:
(i) A list of all products involved; and
(ii) A full description of the manufacturing and controls changes including: the manufacturing site(s) or area(s) involved; the date the change was made; a cross-reference to relevant validation protocols and/or SOP's; and relevant data from studies and tests performed to evaluate the effect of the change on the identity, strength, quality, purity, or potency of the product as they may relate to the safety or effectiveness of the product.

(4) The applicant shall submit the report to the FDA office responsible for reviewing the application. The report shall include all the information required under this paragraph for each change made during the annual reporting interval which ends on the anniversary date in the order in which they were implemented.

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

(f) Labeling changes. (1) Labeling changes requiring supplement submission—FDA approval must be obtained before distribution of the product with the labeling change. Except as described in paragraphs (f)(2) and (f)(3) of this section, an applicant shall submit a supplement describing a proposed change in the package insert, package label, container label, or, if applicable, a Medication Guide required under part 208 of this chapter incorporating the following changes in an annual report submitted to FDA each year as provided in paragraph (d)(1) of this section:

   (A) Editorial or similar minor changes;
   (B) A change in the information on how the product is supplied that does not involve a change in the dosage strength or dosage form; and
   (C) A change in the information specified in §208.29(b)(8)(iii) and (b)(8)(iv) of this chapter for a Medication Guide.

   (ii) The applicant may distribute a product with a package insert, package label, or container label bearing such change at the time the change is made.

   (2) Labeling changes requiring supplement submission—product with a labeling change that may be distributed before FDA approval. (1) An applicant shall submit, at the time such change is made, a supplement for any change in the package insert, package label, or container label to accomplish any of the following:

      (A) To add or strengthen a contraindication, warning, precaution, or adverse reaction;
      (B) To add or strengthen a statement about abuse, dependence, psychological effect, or overdosage;
      (C) To add or strengthen an instruction about dosage and administration that is intended to increase the safety of the use of the product; and
      (D) To delete false, misleading, or unsupported indications for use or claims for effectiveness.

      (ii) Pending approval of the supplement by FDA, the applicant may distribute a product with a package insert, package label, or container label bearing such change at the time the supplement is submitted. The supplement shall clearly identify the change being made and include necessary supporting data. The supplement and its mailing cover shall be plainly marked: "Special Labeling Supplement—Changes Being Effected."

(3) Labeling changes requiring submission in an annual report. (i) An applicant shall submit any final printed package insert, package label, 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; and
   (C) A change in the information specified in §208.29(b)(8)(iii) and (b)(8)(iv) of this chapter for a Medication Guide.

   (ii) The applicant may distribute a product with a package insert, package label, or container label bearing such change at the time the change is made.
§ 601.15 Advertisements and promotional labeling. Advertisements and promotional labeling shall be submitted to the Center for Biologics Evaluation and Research in accordance with the requirements set forth in §314.81(b)(3)(i) of this chapter, except that Form FDA–2567 (Transmittal of Labels and Circulators) or an equivalent form shall be used.

(g) Failure to comply. In addition to other remedies available in law and regulations, in the event of repeated failure of the applicant to comply with this section, FDA may require that the applicant submit a supplement for any proposed change and obtain approval of the supplement by FDA prior to distribution of the product made using the change.

(h) Administrative review. Under §10.75 of this chapter, an applicant may request internal FDA review of FDA employee decisions under this section.

§ 601.15 Foreign establishments and products: samples for each importation.

Random samples of each importation, obtained by the District Director of Customs and forwarded to the Director, Center for Biologics Evaluation and Research, shall be at least two final containers of each lot of product. A copy of the associated documents which describe and identify the shipment shall accompany the shipment for forwarding with the samples to the Director, Center for Biologics Evaluation and Research. For shipments of 20 or less final containers, samples need not be forwarded, provided a copy of an official release from the Center for Biologics Evaluation and Research accompanies each shipment.

§ 601.20 Biologics licenses; issuance and conditions.

(a) Examination—compliance with requirements. A biologics license application shall be approved only upon examination of the product and upon a determination that the product complies with the standards established in the biologics license application and the requirements prescribed in the regulations in this chapter including but not limited to the good manufacturing practice requirements set forth in parts 210, 211, 600, 606, and 820 of this chapter.

(b) Availability of product. No biologics license shall be issued unless:

(1) The product intended for introduction into interstate commerce is available for examination, and

(2) Such product is available for inspection during all phases of manufacture.

(c) Manufacturing process—impairment of assurances. No product shall be licensed if any part of the process of or relating to the manufacture of such product, in the judgment of the Director, Center for Biologics Evaluation and Research, would impair the assurances of continued safety, purity, and potency as provided by the regulations contained in this chapter.

(d) Inspection—compliance with requirements. A biologics license shall be issued or a biologics license application approved only after inspection of the establishment(s) listed in the biologics license application and upon a determination that the establishment(s) complies with the standards established in the biologics license application and the requirements prescribed in applicable regulations.

(e) One biologics license to cover all locations. One biologics license shall be issued to cover all locations meeting the establishment standards identified in the approved biologics license application and each location shall be subject to inspection by FDA officials.

§ 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,
Food and Drug Administration, HHS


[64 FR 56451, Oct. 20, 1999]

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

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


§ 601.25 Review procedures to determine that licensed biological products are safe, effective, and not misbranded under prescribed, recommended, or suggested conditions of use.

For purposes of reviewing biological products that have been licensed prior to July 1, 1972, to determine that they are safe and effective and not misbranded, the following regulations shall apply. Prior administrative action exempting biological products from the provisions of the Federal Food, Drug, and Cosmetic Act is superseded to the extent that these regulations result in imposing requirements pursuant to provisions therein for a designated biological product or category of products.

(a) Advisory review panels. The Commissioner of Food and Drugs shall appoint advisory review panels (1) to evaluate the safety and effectiveness of biological products for which a license has been issued pursuant to section 351 of the Public Health Service Act, (2) to review the labeling of such biological products, and (3) to advise him on which of the biological products under review are safe, effective, and not misbranded. An advisory review panel shall be established for each designated category of biological product. The members of a panel shall be qualified experts, appointed by the Commissioner, and shall include persons from lists submitted by organizations representing professional, consumer, and industry interests. Such persons shall represent a wide divergence of responsible medical and scientific opinion. The Commissioner shall designate the chairman of each panel, and summary minutes of all meetings shall be made.

(b) Request for data and views. (1) The Commissioner of Food and Drugs will publish a notice in the Federal Register requesting interested persons to submit, for review and evaluation by an advisory review panel, published and unpublished data and information.
§601.25 21 CFR Ch. I (4–1–03 Edition)

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 biologicals under review and the full report or reports of the panel. Thirty days thereafter such data and information shall be made publicly available and may be viewed at the Dockets Management Branch of the Food and Drug Administration, except to the extent that the person submitting it demonstrates that it still falls within the confidentiality provisions of one or more of those statutes.

(3) To be considered, 12 copies of the submission on any marketed biological product within the class shall be submitted, preferably bound, indexed, and on standard sized paper, approximately 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 efficacy of each individual active component.

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 as to the efficacy of combinations of the individual active components.

5. Pertinent medical and scientific literature.

B. Combinations of the individual active components.

1. Controlled studies.

2. Partially controlled or uncontrolled studies.

3. Documented case reports.

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

5. Pertinent medical and scientific literature.

C. Finished biological product.

1. Controlled studies.

2. Partially controlled or uncontrolled studies.

3. Documented case reports.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

(3) A statement which designates those biological products determined by the panel not to fall within either paragraph (e) (1) or (2) of this section on the basis of the panel’s conclusion that the available data are insufficient to classify such biological products, and for which further testing is therefore required. The report shall recommend with as much specificity as possible the type of further testing required and the time period within which it might reasonably be concluded. The report shall also recommend whether the product license should or should not be revoked, thus permitting or denying continued manufacturing and marketing of the biological product pending completion of the testing. This recommendation will be based on an assessment of the present evidence of the safety and effectiveness of the product and the potential benefits and risks likely to result from the continued use of the product for a limited period of time while the questions raised concerning the product are being resolved by further study.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

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

§ 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

VerDate Jan<31>2003 08:07 Apr 12, 2003 Jkt 200069 PO 00000 Frm 00031 Fmt 8010 Sfmt 8010 Y:\SGML\200069T.XXX 200069T

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.
§ 601.26 21 CFR Ch. I (4–1–03 Edition)

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.

(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)(3) 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
Food and Drug Administration, HHS

§ 601.27

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 can be given and that a clear opportunity to refuse is presented.

(g) Court appeal. The final order(s) published pursuant to paragraph (e) of this section constitute final agency action from which appeal lies to the courts. The Food and Drug Administration will request consolidation of all appeals in a single court. Upon court appeal, the Commissioner of Food and Drugs may, at the Commissioner’s discretion, stay the effective date for part or all of the final order or notice, pending appeal and final court adjudication.

(h) [Reserved]

(i) Institutional review and informed consent. Information and data submitted under this section after July 27, 1981, shall include statements regarding each clinical investigation involving human subjects, that it was conducted in compliance with the requirements for informed consent under part 50 of this chapter. Such a study is also subject to the requirements for institutional review under part 56 of this chapter, unless exempt under § 56.104 or § 56.105.


§ 601.27 Pediatric studies.

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

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

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

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

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

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

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

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

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

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

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

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

[63 FR 66671, Dec. 2, 1998]

§ 601.28 Annual reports of postmarketing pediatric studies.

Sponsors of licensed biological products shall submit the following information each year within 60 days of the anniversary date of approval of the license to the Director, Center for Biologics Evaluation and Research:

(a) Summary. A brief summary stating whether labeling supplements for pediatric use have been submitted and whether new studies in the pediatric population to support appropriate labeling for the pediatric population have been initiated. Where possible, an estimate of patient exposure to the drug product, with special reference to the pediatric population (neonates, infants, children, and adolescents) shall be provided, including dosage form.

(b) Clinical data. Analysis of available safety and efficacy data in the pediatric population and changes proposed in the labeling based on this information. An assessment of data needed to ensure appropriate labeling for the pediatric population shall be included.

(c) Status reports. A statement on the current status of any postmarketing studies in the pediatric population performed by, or on behalf of, the applicant. The statement shall include whether postmarketing clinical studies in pediatric populations were required or agreed to, and, if so, the status of these studies shall be reported to FDA in annual progress reports of postmarketing studies under §601.70 rather than under this section.


§ 601.29 Guidance documents.

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

(b) The Center for Biologics Evaluation and Research (CBER) maintains a list of guidance documents that apply to the center’s regulations. The lists are maintained on the Internet and are published annually in the FEDERAL REGISTER. You may request a copy of the CBER list from the Office of Communication, Training, and Manufacturers Assistance (HFM–40), Center for Biologics Evaluation and Research, Food and Drug Administration, 1401 Rockville Pike, Rockville, MD 20852–1448.

[65 FR 56480, Sept. 19, 2000]

Subpart D—Diagnostic Radiopharmaceuticals

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.
(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 §§601.40 and 601.42, FDA may withdraw approval, following a hearing as provided in part 15 of this chapter, as modified by this section, if:

(1) A postmarketing clinical study fails to verify clinical benefit;
(2) The applicant fails to perform the required postmarketing study with due diligence;
(3) Use after marketing demonstrates that postmarketing restrictions are inadequate to ensure safe use of the biological product;
(4) The applicant fails to adhere to the postmarketing restrictions agreed upon;
(5) The promotional materials are false or misleading; or
(6) Other evidence demonstrates that the biological product is not shown to be safe or effective under its conditions of use.

(b) Notice of opportunity for a hearing. The Director of the Center for Biologics Evaluation and Research will give the applicant notice of an opportunity for a hearing on the Center’s proposal to withdraw the approval of an application approved under §601.40 or §601.41. The notice, which will ordinarily be a letter, will state generally the reasons for the action and the proposed grounds for the order.

(c) Submission of data and information.

(1) If the applicant fails to file a written request for a hearing within 15 days of receipt of the notice, the applicant waives the opportunity for a hearing.

(2) If the applicant files a timely request for a hearing, the agency will publish a notice of hearing in the Federal Register in accordance with §§12.32(e) and 15.20 of this chapter.

(3) An applicant who requests a hearing under this section must, within 30 days of receipt of the notice of opportunity for a hearing, submit the data and information upon which the applicant intends to rely at the hearing.

(d) Separation of functions. Separation of functions (as specified in §10.55 of this chapter) will not apply at any point in withdrawal proceedings under this section.

(e) Procedures for hearings. Hearings held under this section will be conducted in accordance with the provisions of part 15 of this chapter, with the following modifications:

(1) An advisory committee duly constituted under part 14 of this chapter will be present at the hearing. The committee will be asked to review the issues involved and to provide advice and recommendations to the Commissioner of Food and Drugs.

(2) The presiding officer, the advisory committee members, up to three representatives of the applicant, and up to three representatives of the Center may question any person during or at the conclusion of the person’s presentation. No other person attending the hearing may question a person making a presentation. The presiding officer may, as a matter of discretion, permit questions to be submitted to the presiding officer for response by a person making a presentation.

(f) Judicial review. The Commissioner’s decision constitutes final agency action from which the applicant may petition for judicial review. Before requesting an order from a court for a stay of action pending review, an applicant must first submit a petition for a stay of action under §10.35 of this chapter.

§ 601.44 Postmarketing safety reporting.

Biological products approved under this program are subject to the postmarketing recordkeeping and safety
Food and Drug Administration, HHS

§ 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 4656, Dec. 24, 1974]

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

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

(b) The existence of a biological product file will not be disclosed by the Food and Drug Administration before a biologics license application has been approved unless it has previously been publicly disclosed or acknowledged. The Director of the Center for Biologics Evaluation and Research will maintain a list available for public disclosure of biological products for which a license application has been approved.

(c) If the existence of a biological product file has not been publicly disclosed or acknowledged, no data or information in the biological product file is available for public disclosure.

(d)(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
§ 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), pending issue, e.g., at an open session of a Food and Drug Administration advisory committee or pursuant to an exchange of important regulatory information with a foreign government.

(2) Notwithstanding paragraph (d)(1) of this section, FDA will make available to the public upon request the information in the IND that was required to be filed in Docket Number 95S–0158 in the Dockets Management Branch (HFA–305), Food and Drug Administration, 12420 Parklawn Dr., rm. 1–23, Rockville, MD 20857, for investigations involving an exception from informed consent under § 50.24 of this chapter. Persons wishing to request this information shall submit a request under the Freedom of Information Act.

(e) After a license has been issued, the following data and information in the biological product file are immediately available for public disclosure unless extraordinary circumstances are shown:

(1) All safety and effectiveness data and information.

(2) A protocol for a test or study, unless it is shown to fall within the exemption established for trade secrets and confidential commercial or financial information in § 20.61 of this chapter.

(3) Adverse reaction reports, product experience reports, consumer complaints, and other similar data and information, after deletion of:

(i) Names and any information that would identify the person using the product.

(ii) Names and any information that would identify any third party involved with the report, such as a physician or hospital or other institution.

(4) A list of all active ingredients and any inactive ingredients previously disclosed to the public, as defined in § 20.81 of this chapter.

(5) An assay method or other analytical method, unless it serves no regulatory or compliance purpose and it is shown to fall within the exemption established in § 20.61 of this chapter.

(6) All correspondence and written summaries of oral discussions relating to the biological product file, in accordance with the provisions of part 20 of this chapter.

(7) All records showing the manufacturer’s testing of a particular lot, after deletion of data or information that would show the volume of the drug produced, manufacturing procedures and controls, yield from raw materials, costs, or other material falling within § 20.61 of this chapter.

(8) All records showing the testing 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.
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

(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.

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.

(c) When to report. Annual progress reports for postmarketing study commitments entered into by applicants shall be reported to FDA within 60 days.
of the anniversary date of the U.S. approval of the application for the product.

(d) Where to report. Submit two copies of the annual progress report of postmarketing studies to the Food and Drug Administration, Center for Biologics Evaluations and Research, Document Control Center (HFM-99), 1401 Rockville Pike, Rockville, MD 20852–1448.

(e) Public disclosure of information. Except for the information described in this paragraph, FDA may publicly disclose any information concerning a postmarketing study, within the meaning of this section, if the agency determines that the information is necessary to identify an applicant or to establish the status of the study including the reasons, if any, for failure to conduct, complete, and report the study. Under this section, FDA will not publicly disclose trade secrets, as defined in §20.61 of this chapter, or information, described in §20.63 of this chapter, the disclosure of which would constitute an unwarranted invasion of personal privacy.

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

§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 (CBER) will give the applicant notice of an opportunity for a hearing on CBER’s 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.
§ 601.93

(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.

§ 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 §§601.81(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.
§ 606.20 Labeling, general requirements.

606.120 Container label.

606.122 Instruction circular.

Subpart G—Finished Product Control

Subpart H—Laboratory Controls

606.140 Laboratory controls.

606.151 Compatibility testing.

Subpart I—Records and Reports

606.160 Records.

606.165 Distribution and receipt; procedures and records.

606.170 Adverse reaction file.

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


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 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.

(3) 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.

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.


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, platelethpheresis 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:

<table>
<thead>
<tr>
<th>Equipment</th>
<th>Performance check</th>
<th>Frequency</th>
<th>Frequency of calibration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Temperature recorder</td>
<td>Compare against thermometer</td>
<td>Daily</td>
<td>As necessary.</td>
</tr>
<tr>
<td>Refrigerated centrifuge</td>
<td>Observe speed and temperature</td>
<td>Each day of use</td>
<td>Do.</td>
</tr>
</tbody>
</table>
Food and Drug Administration, HHS

§ 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:

<table>
<thead>
<tr>
<th>Reagent or solution</th>
<th>Frequency of testing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-human globulin</td>
<td>Each day of use.</td>
</tr>
<tr>
<td>Blood grouping reagents</td>
<td>Do.</td>
</tr>
<tr>
<td>Lectins</td>
<td>Do.</td>
</tr>
<tr>
<td>Antibody screening and reverse grouping cells</td>
<td>Do.</td>
</tr>
<tr>
<td>Hepatitis test reagents</td>
<td>Each run.</td>
</tr>
<tr>
<td>Syphilis serology reagents</td>
<td>Do.</td>
</tr>
<tr>
<td>Enzymes</td>
<td>Each day of use.</td>
</tr>
</tbody>
</table>

(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.

(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.

§ 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 in accordance with §610.46 of this chapter to look at prior donations of Whole Blood, blood components, Source Plasma and Source Leukocytes from a donor who has donated blood and subsequently tests repeatedly reactive for antibody to human immunodeficiency virus (HIV) or otherwise is determined to be unsuitable when tested in accordance with §610.45 of this chapter. Procedures to quarantine in-house Whole Blood, blood components, Source Plasma and
§ 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.
§ 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 (except Source Plasma) by all blood establishments.

(b) The label provided by the collecting facility and the initial processing facility shall not be removed, altered, or obscured, except that the label may be altered to indicate the proper name and other information required to identify accurately the contents of a container after blood components have been prepared.

(c) The container label shall 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, and modifier(s), if appropriate.

(2) The name, address, registration number, and, if a licensed product, the license number of each manufacturer.

(3) The donor, pool, or lot number relating the unit to the donor.

(4) The expiration date, including the day, month, and year, and, if the dating period for the product is 72 hours or less, the hour of expiration.

(5) If the product is intended for transfusion, the appropriate donor classification statement, i.e., “paid donor” or “volunteer donor”, in no less prominence than the proper name of the product.

(6) 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 range within reasonable limits.

(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.”

(9) The statement: “This product may transmit infectious agents.”

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

(11) The statement: “Caution: For Manufacturing Use Only”, when applicable.

(12) If the product is intended for transfusion, the ABO and Rh groups of the donor shall be designated conspicuously. For Cryoprecipitated AHF, the Rh group may be omitted. The Rh group shall be designated as follows:

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

(ii) If the test using Anti-D Blood Grouping Reagent is negative but the test for D+ is positive, the product shall be labeled: “Rh positive.”

(iii) If the test using Anti-D Blood Grouping Reagent is negative and the test for D+ is negative, the product shall be labeled: “Rh negative.”

(13) The container label may bear encoded information in the form of machine-readable symbols approved for use by the Director, Center for Biologics Evaluation and Research (HFB–1).

(d) Except for recovered plasma intended for manufacturing use or as otherwise approved by the Director, Center for Biologics Evaluation and Research (HFB–1), the paper of the container label shall be white and print shall be solid black, with the following additional exceptions:

(1) The Rh blood group shall be printed as follows:

(i) Rh positive: Use black print on white background.
(ii) Rh negative: Use white print on black background.

(2) The proper name of the product, any appropriate modifier(s), the donor classification statement, and the statement “properly identify intended recipient” shall be printed in solid red or in solid black.

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

<table>
<thead>
<tr>
<th>Blood group</th>
<th>Color of label paper</th>
</tr>
</thead>
<tbody>
<tr>
<td>O</td>
<td>Blue</td>
</tr>
<tr>
<td>A</td>
<td>Yellow</td>
</tr>
<tr>
<td>B</td>
<td>Pink</td>
</tr>
<tr>
<td>AB</td>
<td>White</td>
</tr>
</tbody>
</table>

(4) Ink colors used for the optional color coding system described in paragraph (d)(3) of this section shall be a visual match to specific color samples designated by the Director, Center for Biologics Evaluation and Research (HFB–1).

(5) Special labels, such as those described in paragraphs (h) and (i) of this section, may be color coded using the colors recommended in the guideline (see paragraph (a) of this section), or colors otherwise approved for use by the Director, Center for Biologics Evaluation and Research (HFB–1).

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

(1) Whole Blood labels shall include:

(i) The volume of anticoagulant.

(ii) The name of the applicable anticoagulant immediately preceding and of no less prominence than the proper name approved for use by the Director, Center for Biologics Evaluation and Research.

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

(2) Except for frozen, deglycerolized, or washed Red Blood Cell products, red blood cell labels shall include:

(i) The volume and kind of Whole Blood, including the type of anticoagulant, from 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) Labels for products with a dating period of 72 hours or less, including any product prepared in a system that may compromise sterility, shall bear the hour of expiration.

(4) If tests for unexpected antibodies are positive, Plasma intended for transfusion shall be labeled: “Contains (name of antibody).”

(5) Recovered plasma labels shall include:

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

(ii) The statement as applicable: “Caution: For Manufacturing Use Only”; or “Caution: For Use in Manufacturing Noninjectable Products Only.” If the recovered plasma has a reactive screening test for evidence of infection due to a communicable disease agent(s) under §610.40 of this chapter, or is collected from a donor with a previous record of a reactive screening test for evidence of infection due to a communicable disease agent(s) under §610.40 of this chapter, the recovered plasma must be labeled as required under §610.40(h)(2)(i)(E) of this chapter.

(iii) For recovered plasma not meeting the requirements for manufacture into licensable products, the statement: “Not for Use in Products Subject to License Under Section 361 of the Public Health Service Act.”

(f) Blood and blood components determined to be unsuitable for transfusion shall be prominently labeled: “NOT FOR TRANSFUSION”, and the label shall state the reason the unit is considered unsuitable. The provision does not apply to recovered plasma labeled according to paragraph (e)(5) of this section.

(g) [Reserved]

(h) The following additional information shall appear on the label for blood or blood components shipped in an emergency, prior to completion of required tests, in accordance with §640.2(f) 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 and not completed before shipment.

(i) The following additional information shall appear on the label for Whole Blood or Red Blood Cells intended for autologous infusion:

(1) Information adequately identifying the patient, e.g., name, blood group, hospital, and identification number.

(2) Date of donation.

(3) The statement: “FOR AUTOLOGOUS USE ONLY.”

(4) In place of the blood group label, each container of blood 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 in the hepatitis tests prescribed under §610.40 of this chapter shall be prominently and permanently labeled: “FOR AUTOLOGOUS USE ONLY.”

(5) Units of blood originally intended for autologous use, except those labeled as prescribed under paragraph (i)(4) of this section, may be issued for homologous 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 paragraph (i) (1), (2), and (3) of this section shall be removed or otherwise obscured.

(j) A tie-tag attached to the container may be used for providing the information required by paragraph (e) (1)(iii), (2)(ii), and (4), (h), or (1)(1), (2), and (3) of this section.


EFFECTIVE DATE NOTE: The information collection requirements contained in §606.121 will not become effective until OMB approval has been obtained. FDA will publish a notice of OMB approval in the Federal Register.

§ 606.122 Instruction circular.

An instruction circular shall be available for distribution if the product is intended for transfusion. The instruction circular shall 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) Statements that the product was prepared from blood that was negative when tested for antibody to Human Immunodeficiency Virus (HIV) and nonreactive for hepatitis B surface antigen by FDA required tests and nonreactive when tested for syphilis by a serologic test for syphilis (STS).

(f) The statements: “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, contraindications, side effects and hazards, dosage and administration recommendations.

(j) [Reserved]

(k) For Red Blood Cells, the instruction circular shall contain:

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


(l) For Platelets, the instruction circular shall 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 instruction circular shall 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 between 30 and 37 °C.
(3) When applicable, instructions to begin administration of the product within 6 hours after thawing.
(4) Instructions to administer to ABO-group-compatible recipients.
(5) A statement that this product has the same hepatitis risk as Whole Blood; other plasma volume expanders without this risk are available for treating hypovolemia.
(n) For Cryoprecipitated AHF, the instruction circular shall 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.”

§ 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.

§ 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 of 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 of quarantine, notification, testing, and disposition performed pursuant to §§ 610.46 and 610.47 of this chapter.
   (ix) Records of notification of donors deferred or determined not to be suitable for donation, including appropriate followup if the initial 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) 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. The retention period shall be no less than 5 years after the records of processing have been completed or 6 months after the latest expiration date for the individual product, whichever is a 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.

§ 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, Center for Biologics Evaluation and Research, shall be notified by telephone, facsimile, express mail, or electronically transmitted mail as soon as possible; a written report of the investigation shall be submitted to the Director, Office of Compliance and Biologics Quality, Center for Biologics Evaluation and Research, 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.

§ 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), 1401 Rockville Pike, suite 200N, Rockville MD, 20852–1448 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]
Subpart C—Procedures for Foreign Blood Product Establishments

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

Subpart D—Exemptions

607.65 Exemptions for blood product establishments.


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

Subpart A—General Provisions

§ 607.3 Definitions.


(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.

§ 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), 1401 Rockville Pike, suite 200N, Rockville, MD 20852–1448, 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), 1401 Rockville Pike, suite 200N, Rockville, MD 20852–1448.


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), 1401 Rockville Pike, suite 200N, Rockville, MD 20852–1448, 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.

§ 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.

§ 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.

§ 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
§ 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) [Reserved]

[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, 1401 Rockville Pike, suite 200N, Rockville, MD 20852–1448. 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
Food and Drug Administration, HHS

§ 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...
§ 607.65

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 approved for Medicare reimbursement and 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.


PART 610—GENERAL BIOLOGICAL PRODUCTS STANDARDS

Subpart A—Release Requirements

Sec.

610.1 Tests prior to release required for each lot.

610.2 Requests for samples and protocols; official release.

Subpart B—General Provisions

610.9 Equivalent methods and processes.

610.10 Potency.

610.11 General safety.

610.11a Inactivated influenza vaccine, general safety test.

610.12 Sterility.

610.13 Purity.

610.14 Identity.

610.15 Constituent materials.

610.16 Total solids in serums.

610.17 Permissible combinations.

610.18 Cultures.

610.19 Status of specific products; Group A streptococcus.
Subpart C—Standard Preparations and Limits of Potency

610.20 Standard preparations.
610.21 Limits of potency.

Subpart D—Mycoplasma

610.30 Test for Mycoplasma.

Subpart E—Testing Requirements for Communicable Disease Agents

610.40 Test requirements.
610.41 Donor deferral.
610.42 Restrictions on use for further manufacture of medical devices.
610.44 Use of reference panels by manufacturers of test kits.
610.46 “Lookback” requirements.
610.47 “Lookback” notification requirements for transfusion services.

Subpart F—Dating Period Limitations

610.50 Date of manufacture.
610.53 Dating periods for licensed biological products.

Subpart G—Labeling Standards

610.60 Container label.
610.61 Package label.
610.62 Proper name; package label; legible type.
610.63 Divided manufacturing responsibility to be shown.
610.64 Name and address of distributor.
610.65 Products for export.


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 comple-

§ 610.2 Requests for samples and protocols; official release.

(a) General. Samples of any lot of any licensed product, except for radioactive biological products, 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. 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) Radioactive biological products. Samples of any lot of a radioactive biological product, as defined in §600.3(ee) of this chapter, together with the protocols showing results of applicable tests, may at any time be required to be sent to the Food and Drug Administration for official release. Upon notification by the Director, Center for Drug Evaluation and Research, a manufacturer shall not distribute a lot of a radioactive 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.

§ 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, Food and Drug Administration, 1401 Rockville Pike, Rockville, MD 20852-1448.


§ 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 by the Director, Center for Biologics Evaluation and Research, 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 approved by the Director, Center for Biologics Evaluation and Research, 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) [Reserved]


EFFECTIVE DATE NOTE: At 68 FR 10160, Mar. 4, 2003, §610.11 was amended by adding paragraph (g)(2), effective May 5, 2003. For the convenience of the user the added text follows:

§ 610.11 General safety.

* * * * *

(g) * * *

(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, 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, 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.

§ 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.

Except as provided in paragraphs (f) and (g) of this section, the sterility of each lot of each product shall be demonstrated by the performance of the tests prescribed in paragraphs (a) and (b) of this section for both bulk and final container material.

(a) The test. Bulk material shall be tested separately from final container material and material from each final container shall be tested in individual test vessels as follows:

(1) Using Fluid Thioglycollate Medium. (i) Bulk and final container material. The volume of product, as required by paragraph (d) of this section (hereinafter referred to also as the “inoculum”), from samples of both bulk and final container material, shall be inoculated into test vessels of Fluid Thioglycollate Medium. The inoculum and medium shall be mixed thoroughly and incubated at a temperature of 30 to 35 °C for a test period of no less than 14 days and examined visually for evidence of growth on the third, fourth, or fifth day, and on the seventh or eighth day, and on the last day of the test period. Results of each examination shall be recorded. If the inoculum renders the medium turbid so that the absence of growth cannot be determined reliably by visual examination, portions of this turbid medium in amounts of no less than 1.0 milliliter shall be transferred on the third, fourth, or fifth day of incubation, from each of the test vessels and inoculated into additional vessels of the medium. The material in the additional vessels shall be incubated at a temperature of 30 to 35 °C for no less than 14 days. Notwithstanding such transfer of material, examination of the original vessels shall be continued as prescribed above. The additional test vessels shall be examined visually for evidence of growth on the third, fourth, or fifth day of incubation, and on the seventh or eighth day, and on the last day of the incubation period. If growth appears, repeat tests may be performed as prescribed in paragraph (b) of this section and interpreted as specified in paragraph (c) of this section.

(ii) Final container material containing a mercurial preservative. In addition to the test prescribed in paragraph (a)(1)(i) of this section, final container material containing a mercurial preservative shall be tested using Fluid Thioglycollate Medium following the procedures prescribed in such subparagraph, except that the incubation shall be at a temperature of 20 to 25 °C.

(2) Using Soybean-Casein Digest Medium. Except for products containing a mercurial preservative, a test shall be made on final container material, following the procedures prescribed in paragraph (a)(1)(i) of this section, except that the medium shall be Soybean-Casein Digest Medium and the incubation shall be at a temperature of 20 to 25 °C.

(b) Repeat tests. If growth appears in any of the test media during testing of either bulk or final container material, the test may be repeated to rule out faulty test procedures as follows:

(1) Repeat bulk test. Only one repeat bulk test may be conducted. The volume of inoculum to be used for the repeat bulk test shall be as prescribed in paragraph (d)(1) of this section. The repeat test shall be performed using the procedure prescribed in paragraph (a)(1)(i) of this section.

(2) First repeat final container test. The number of test samples and the volumes of product used for the first repeat test shall be as prescribed in paragraph (d)(2) of this section. For products that do not contain a mercurial preservative, the repeat test shall be performed, using both Fluid Thioglycollate Medium and Soybean-Casein Digest Medium, following the procedures prescribed in paragraphs (a)(1)(i) and (a)(2), respectively, of this section. If the product contains a mercurial preservative, the repeat test shall be performed using Fluid Thioglycollate Medium and the procedures prescribed in paragraphs (a)(1)(i) and (ii) of this section.

(3) Second repeat final container test. If growth appears in any of the first repeat final container tests, all tests of the first repeat final container test shall be repeated, provided there was no evidence of growth in any test of
the bulk material. The test samples used for the second repeat final container test shall be twice the number used for the first repeat final container test.

(c) Interpretation of test results. The results of all tests performed on a lot shall be considered in determining whether or not the lot meets the requirements for sterility, except that tests may be excluded when demonstrated by adequate controls to be invalid. The lot meets the test requirements if no growth appears in the tests prescribed in paragraph (a) of this section. If repeat tests are performed, the lot meets the test requirements if no growth appears in the tests prescribed in paragraph (b)(2) or (3) of this section, whichever is applicable.

(d) Test samples and volumes—(1) Bulk. Each sample for the bulk sterility test shall be representative of the bulk material and the volume tested shall be no less than 10 ml. (Note exceptions in paragraph (g) of this section.)

(2) Final containers. The sample used for each test medium or each incubation temperature of a test medium for the final container and first repeat final container test shall be no less than 20 final containers from each filling of each lot, selected to represent all stages of filling from the bulk vessel. If the amount of material in the final container is 1.0 milliliter or less, the entire contents shall be tested. If the amount of material in the final container is more than 1.0 milliliter, the volume tested shall be the largest single dose recommended by the manufacturer or 1.0 milliliter, whichever is larger, but no more than 10 milliliters of material or the entire contents from a single final container need be tested. If more than 2 filling machines, each with either single or multiple filling stations, are used for filling one lot, no less than 10 filled containers shall be tested from each filling machine for each test medium or each incubation temperature condition, but no more than 100 containers of each lot need be tested. The items tested shall be representative of each filling assembly and shall be selected to represent all stages of the filling operation. (Note exceptions in paragraph (g) of this section.)

(e) Culture medium—(1) Formulae. (i) The formula for Fluid Thioglycollate Medium is as follows:

**FLUID THIOGLYCOLLATE MEDIUM**

<table>
<thead>
<tr>
<th>Component</th>
<th>Quantity</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-cystine</td>
<td>0.5 gm.</td>
</tr>
<tr>
<td>Sodium chloride</td>
<td>2.5 gm.</td>
</tr>
<tr>
<td>Dextrose (C₆H₁₂O₆)</td>
<td>5.5 gm.</td>
</tr>
<tr>
<td>Granular agar (less than 15% moisture by weight)</td>
<td>0.75 gm.</td>
</tr>
<tr>
<td>Yeast extract (water-soluble)</td>
<td>5.0 gm.</td>
</tr>
<tr>
<td>Pancreatic digest of casein</td>
<td>15.0 gm.</td>
</tr>
<tr>
<td>Purified water</td>
<td>1,000.0 ml</td>
</tr>
<tr>
<td>Sodium thioglycollate (or thiglycolic acid—0.3 ml)</td>
<td>0.5 gm.</td>
</tr>
<tr>
<td>Resazurin (0.10% solution, 1.0 ml) (freshly prepared)</td>
<td>0.5 ml.</td>
</tr>
</tbody>
</table>

pH after sterilization 7.1±0.2

(ii) The formula for Soybean-Casein Digest Medium is as follows:

**SOYBEAN-CASEIN DIGEST MEDIUM**

Papain Digest of Soybean Meal | 17.0 gm. |
Dibasic Potassium Phosphate | 3.0 gm.  |
Sodium Chloride              | 5.0 gm.  |
Dextrose (C₆H₁₂O₆)            | 2.5 gm.  |
Pancreatic digest of casein   | 15.0 gm. |
Purified water                | 1,000.0 ml |

pH after sterilization 7.3±0.2

(2) Culture media requirements—(i) Definition of a lot of culture medium and test requirements. A lot of culture medium is that quantity of uniform material identified as having been thoroughly mixed in a single vessel, dispensed into a group of vessels of the same composition and design, sterilized in a single autoclave run, and identified in a manner to distinguish one lot from another. Each lot of culture medium shall be tested for its growth-promoting qualities unless it meets the exception for dehydrated culture medium described in this subpart. The growth-promoting quality test shall be performed on the smallest sized vessel used in an autoclave run. When using a single batch of dehydrated culture medium, a manufacturer need not perform growth-promoting tests on each lot of prepared liquid medium, provided that a validation program exists for autoclaves used to sterilize the culture medium, and the manufacturer has received approval for this practice from the Director, Center for Biologics Evaluation and Research.

(ii) Test organisms, strains, characteristics, identity, and verification. Two or more strains of microorganisms that are exacting in their nutritive and aerobic/anaerobic requirements shall be used to test the growth-promoting...
§ 610.12  21 CFR Ch. I (4–1–03 Edition)

qualities of each lot of test medium. When using Fluid Thioglycollate medium, both an aerobic and an anaerobic test microorganism shall be chosen. When using Soybean Casein Digest Medium, the yeast, *Candida albicans*, shall be one of the two test microorganisms chosen. Manufacturers shall choose the strains of microorganisms from the chart in this paragraph.

<table>
<thead>
<tr>
<th>Medium</th>
<th>Test microorganisms</th>
<th>Incubation temperature</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Fluid Thioglycollate</em></td>
<td><em>Spore-formers</em></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1. <em>Bacillus subtilis</em> (ATCC No. 6633)</td>
<td>30 to 35 °C.</td>
</tr>
<tr>
<td></td>
<td>2. <em>Clostridium sporogenes</em> (ATCC No. 11437)</td>
<td>Do.</td>
</tr>
<tr>
<td></td>
<td><em>Non-spor-formers</em></td>
<td></td>
</tr>
<tr>
<td></td>
<td>5. <em>Bacteroides vulgatus</em> (ATCC No. 8482)</td>
<td>Do.</td>
</tr>
<tr>
<td><em>Soybean-Casein Digest</em></td>
<td><em>Spore-formers</em></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1. <em>Bacillus subtilis</em> (ATCC No. 6633)</td>
<td>20 to 25 °C.</td>
</tr>
<tr>
<td></td>
<td><em>Non-spor-formers</em></td>
<td></td>
</tr>
</tbody>
</table>

ATCC strains of microorganisms described in this section are available from the American Type Culture Collection, 12301 Parklawn Dr., Rockville, MD 20852. Periodic tests shall be performed to verify the integrity of the test organisms in accordance with §610.18 (a) and (b). The results of these periodic tests shall be recorded and retained in accordance with §600.12(b) of this chapter.

(iii) Storage and maintenance of cultures of test organisms. Cultures of the test organisms used to determine the growth-promoting qualities of the medium shall be stored in a manner that will prevent cross contamination or loss of identity, at a temperature and by a method that will retain the initial characteristics of the organisms and ensure freedom from contamination and deterioration. If the test organisms are stored in the freeze-dried state, or frozen, they shall be reconstituted or thawed, whichever is applicable, and plated periodically to verify the colony count of the suspension. If the test suspensions are stored in a state other than freeze-dried or frozen, they shall be plated, and a colony count shall be performed at the time of each growth-promoting quality test to assure that not more than 100 organisms are used per test vessel. The results of tests for verification of the colony count shall be recorded and retained in accordance with §600.12(b) of this chapter.

(iv) Storage and condition of media. A medium shall not be used if the extent of evaporation affects its fluidity, nor shall it be reused in a sterility test of the product. Fluid Thioglycollate Medium shall be stored in the dark at room temperature if the vessels are unsealed. Sealed vessels shall be stored at the manufacturer's specified storage temperature. Fluid Thioglycollate Medium shall not be used if more than the upper one-third of the medium has acquired a pink color. The medium may be restored once by heating on a steam bath or in free-flowing steam until the pink color disappears. The design of the test vessel for Fluid Thioglycollate Medium shall provide favorable aerobic and anaerobic conditions for growth of the microorganisms throughout the test period. Soybean-Casein Digest Medium shall be stored in the dark at 20 to 25 °C. Unsealed vessels of either medium may be stored for more than 10 days at the proper temperature, provided they are tested monthly for growth-promotion and found to be satisfactory. Sealed vessels of either medium may be stored at the proper temperature for a period of time not to exceed 1 year, provided they are tested for growth-promotion every 3 months and found to be satisfactory. The results of such testing shall be recorded and retained in accordance with §600.12(b) of this chapter.
(v) Criteria for a satisfactory growth-promoting quality test. (a) One hundred or fewer organisms of each strain tested shall be used. The test is satisfactory if evidence of growth appears within 7 days in all vessels inoculated. If a lot of medium fails to support the growth of any test organism, or if the test results show that more than 100 organisms of a strain were used or are necessary to promote growth in the lot of medium being tested, or if the growth is not a pure culture of the test organism, a second test may be performed. If it fails the second test, the lot of medium shall be rejected.

(b) Inoculated Fluid Thioglycollate Medium shall be incubated at 30 to 35 °C for 7 days. If the test medium is to be used in determining the sterility of a product containing a mercurial preservative, a second test shall be performed in accordance with paragraph (e)(2)(v)(a) of this section, except that the test shall be incubated at 20 to 25 °C for 7 days. Inoculated Soybean-Casein Digest Medium shall be incubated at 20 to 25 °C for 7 days. The sterility of each lot of medium shall be confirmed by the incubation of uninoculated control test vessels for 7 days at the temperature(s) for that particular medium. The lot of medium is satisfactory if no growth is observed in the control test vessels within the incubation period. The tests for growth-promoting qualities of culture media may be performed simultaneously with sterility testing of biological products, provided the sterility test is considered invalid if the test medium shows no growth response.

(vi) Volume of culture medium. The volume of each culture medium shall be determined for each bulk and final container sterility test required for each product. The ratio of the volume of inoculum to the volume of culture medium shall result in a dilution of the product that is not bacteriostatic or fungistatic, except for products to be tested by membrane filtration. The volume of inhibitors or neutralizers of preservatives added should be considered in determining the proper ratio of inoculum/medium. Vessels of the product-medium mixture(s) and control vessels of the medium shall be inoculated with dilutions of cultures of bacteria or fungi which are viable in the product being tested, and incubated at the appropriate temperature for no less than 7 days.

(f) Membrane filtration. Bulk and final container material or products containing oil products in water-insoluble ointments may be tested for sterility using the membrane filtration procedure set forth in the United States Pharmacopeia (23d Revision, 1995), section entitled “Test Procedures Using Membrane Filtration,” pp. 1689 to 1690, which is incorporated by reference in accordance with 5 U.S.C. 552(a) and 1 CFR part 51. Copies are available from the United States Pharmacopeial Convention, Inc., 12601 Twinbrook Pkwy., Rockville, MD 20852, or available for inspection at the Center for Drug Evaluation and Research’s Division of Medical Library, 5600 Fishers Lane, rm. 11B–40, Rockville, MD, or at the Office of the Federal Register, 800 North Capitol St. NW., suite 700, Washington, DC, except that:

(1) The test samples shall conform with paragraph (d) of this section; and
(2) In addition, for products containing a mercurial preservative, the product shall be tested in a second test using Fluid Thioglycollate Medium incubated at 20 to 25°C in lieu of the test in Soybean-Casein Digest Medium.

(g) Exceptions. Bulk and final container material shall be tested for sterility as described above in this section, except as follows:

(1) Different sterility tests prescribed. When different sterility tests are prescribed for a product in this subchapter.
(2) Alternate incubation temperatures. Two tests may be performed as prescribed in paragraph (a)(1)(i) of this section, one test using an incubation temperature of 18 to 22 °C, the other test using an incubation temperature of 30 to 37 °C, in lieu of performing one test using an incubation temperature of 30 to 35 °C, provided that growth-promoting quality tests have been performed at these temperatures.
(3) [Reserved]
(4) Test precluded or not required. (i) The tests prescribed in this section need not be performed for Whole Blood, Cryoprecipitated AHF, Platelets, Red Blood Cells, Plasma, Source Plasma,
§ 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, when deemed not necessary for the continued safety, purity, and potency of the product.

(b) 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.

(8) Diagnostic biological products not intended for injection. For diagnostic biological products not intended for injection, (i) only the Fluid Thioglycollate Medium test incubated at 30 to 35 °C is required, (ii) the volume of material for the bulk test shall be no less than 2.0 milliliters, and (iii) the sample for the final container test shall be no less than three final containers if the total number filled is 100 or less, and, if greater, one additional container for each additional 50 containers or fraction thereof, but the sample need be no more than 10 containers.

(9) Immune globulin preparations. For immune globulin preparations, the test samples from the bulk material and from each final container need be no more than 2.0 ml.
Food and Drug Administration, HHS

§ 610.15

(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.

§ 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; Poliomyelitis 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
§ 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.

(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.

§ 610.19 Status of specific products; Group A streptococcus.

The presence of Group A streptococcus organisms and derivatives of
Group A streptococcus in Bacterial Vaccines and Bacterial Antigens with "No U.S. Standard of Potency" may induce dangerous tissue reactions in humans. Available data demonstrate that they are unsafe as ingredients in products for human use. Group A streptococcus organisms and derivatives of Group A streptococcus are prohibited from Bacterial Vaccines and Bacterial Antigens with "No U.S. Standard of Potency." Any Bacterial Vaccine or Bacterial Antigen with "No U.S. Standard of Potency" containing Group A streptococcus organisms or derivatives of Group A streptococcus in interstate commerce is in violation of section 351 of the Public Health Service Act (42 U.S.C. 262).

[44 FR 1549, Jan. 5, 1979]

§ 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.
H. influenzae Antitoxin.
Oedema Antitoxin.
Pertussis Antitoxin.
Antirabies Serum.
S. enteritidis Antitoxin.
Staphylococcus Antitoxin.
Tetanus Antitoxin.
V. cholerae 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.


§ 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), 50 units of tetanus antitoxin per milliliter.

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]

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 CO₂ in N₂. 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 onto 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 paragraphs (a)(5) and (a)(6) of this section unless:

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:

<table>
<thead>
<tr>
<th>Donor Testing Status</th>
<th>Label</th>
</tr>
</thead>
<tbody>
<tr>
<td>Untested</td>
<td>“DONOR UNTESTED”</td>
</tr>
<tr>
<td>Tests negative</td>
<td>Label as required under §606.121</td>
</tr>
<tr>
<td>Reactive on current collection/reactive in the last 30 days</td>
<td>“BIOHAZARD” legend in §610.40(h)(2)(ii)(B)</td>
</tr>
<tr>
<td>Tested negative within the last 30 days</td>
<td>“DONOR TESTED WITHIN THE LAST 30 DAYS”</td>
</tr>
</tbody>
</table>

(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
§ 610.40

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 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, or § 640.70 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:

<table>
<thead>
<tr>
<th>Type of Medical Device</th>
<th>Label</th>
</tr>
</thead>
<tbody>
<tr>
<td>A medical device other than an in vitro diagnostic reagent</td>
<td>“Caution: For Further Manufacturing Use as a Component of a Medical Device For Which There Are No Alternative Sources”</td>
</tr>
<tr>
<td>An in vitro diagnostic reagent</td>
<td>“Caution: For Further Manufacturing Into In Vitro Diagnostic Reagents For Which There Are No Alternative Sources”</td>
</tr>
</tbody>
</table>

(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)(2) of this chapter.

[66 FR 31162, June 11, 2001]

§ 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.

[66 FR 31164, June 11, 2001]

§ 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,
§ 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 “Lookback” requirements.

(a) Quarantine and notification. (1) All blood and plasma establishments are required to take appropriate action when a donor of Whole Blood, blood components, Source Plasma and Source Leukocytes tests repeatedly reactive for antibody to human immunodeficiency virus (HIV), or otherwise is determined to be unsuitable when tested in accordance with § 610.45. For Whole Blood, blood components, Source Plasma and Source Leukocytes collected from that donor within the 5 years prior to the repeatedly reactive test, if intended for transfusion, or collected within the 6 months prior to the repeatedly reactive test, if intended for further manufacture into injectable products, except those products exempt from quarantine in accordance with § 610.46(c), the blood establishment shall promptly, within 72 hours:

(i) Quarantine all such Whole Blood, blood components, Source Plasma and Source Leukocytes from previous collections held at that establishment; and

(ii) Notify consignees of the repeatedly reactive HIV screening test results so that all Whole Blood, blood components, Source Plasma and Source Leukocytes from previous collections they hold are quarantined.

(2) Consignees notified in accordance with paragraph (a)(1)(ii) of this section shall quarantine Whole Blood, blood components, Source Plasma and Source Leukocytes from previous collections they hold are quarantined.

(b) Further testing and notification of consignees of results. Blood establishments that have collected Whole Blood, blood components, Source Plasma or Source Leukocytes from a donor as described in paragraph (a) of this section shall quarantine Whole Blood, blood components, Source Plasma and Source Leukocytes held at that establishment except as provided in paragraph (c) of this section.

(iii) Further testing and notification of consignees of results. Blood establishments that have collected Whole Blood, blood components, Source Plasma or Source Leukocytes from a donor as described in paragraph (a) of this section shall perform a licensed, more specific test for HIV on the donor’s blood, and in the case of distributed products, further shall notify the consignee(s) of the results of this test, within 30 calendar days after the donor’s repeatedly reactive test. Pending the availability of a licensed, more specific test for HIV–2, a second, different screening test for antibody to HIV–2 shall be used along with a licensed, more specific test for HIV–1.
Food and Drug Administration, HHS

§ 610.50

Exemption from quarantine. Products intended for transfusion need not be held in quarantine if a determination has been made that the Whole Blood, blood components, Source Plasma or Source Leukocytes was collected more than 12 months prior to the donor’s most recent negative antibody screening test when tested in accordance with §610.45. Pooled Source Plasma and Source Leukocytes are exempt from quarantine.

(d) Release from quarantine. Whole Blood, blood components, Source Plasma and Source Leukocytes intended for transfusion or further manufacture which have been quarantined under paragraph (a) of this section may be released if the donor is subsequently tested for antibody to HIV as provided in paragraph (b) of this section and the test result is negative, absent other informative test results.

(e) Actions under this section do not constitute a product recall as defined in §7.3(g) of this chapter.

§ 610.47 “Lookback” notification requirements for transfusion services.

(a) Transfusion services that are not subject to the Health Care Financing Administration’s regulations on conditions of Medicare participation for hospitals (42 CFR part 482) are required to take appropriate action in accordance with paragraphs (b) and (c) of this section when a recipient has received Whole Blood or blood components from a donor determined to be unsuitable when tested for human immunodeficiency virus (HIV) infection in accordance with §610.45 and the results of the additional tests as provided for in §610.46(b) are positive.

(b) Notification of recipients of prior transfusion. If the transfusion service has administered Whole Blood or blood components as described in paragraph (a) of this section, the transfusion service shall notify the recipient’s attending physician (physician of record) and ask him or her to inform the recipient of the need for HIV testing and counseling. If the physician is unavailable or declines to notify the recipient, the transfusion service shall notify the recipient and inform the recipient of the need for HIV testing and counseling. The notification process shall include a minimum of three attempts to notify the recipient and be completed within a maximum 8 weeks of receipt of the result of the licensed, more specific test for HIV. The transfusion service is responsible for notification, including basic explanations to the recipient and referral for counseling, and shall document the notification or attempts to notify the attending physician or the recipient, pursuant to §606.160 of this chapter.

(c) Notification to legal representative or relative. If the transfusion recipient has been adjudged incompetent by a State court, the transfusion service or physician must notify a legal representative designated in accordance with State law. If the transfusion recipient is competent, but State law permits a legal representative or relative to receive the information on the recipient’s behalf, the transfusion service or physician must notify the recipient or his or her legal representative or relative. If the transfusion recipient is deceased, the transfusion service or physician must continue the notification process and inform the deceased recipient’s legal representative or relative. Reasons for notifying the recipient’s relative or legal representative on his or her behalf shall be documented pursuant to §606.160 of this chapter.

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.


79
§ 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.

<table>
<thead>
<tr>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
</tr>
</thead>
<tbody>
<tr>
<td>Product</td>
<td>Manufacturer's storage period 1 to 5 °C (unless otherwise stated)</td>
<td>Manufacturer's storage period 0 °C or colder (unless otherwise stated)</td>
<td>Dating period after leaving manufacturer's storage when stored at 2 to 8 °C (unless otherwise stated)</td>
</tr>
<tr>
<td>Adenovirus Vaccine Live Oral</td>
<td>6 months ................... Not applicable ................... 6 months.</td>
<td>6 months.</td>
<td>6 months.</td>
</tr>
<tr>
<td>Albumin (Human)</td>
<td>3 years ................... do ................... 3 years.</td>
<td>3 years.</td>
<td>3 years.</td>
</tr>
<tr>
<td>Allergenic Extracts labeled “No U.S. Standard of Potency”</td>
<td>1. With 50 percent or more glycerin</td>
<td>3 years ................... do ................... 3 years.</td>
<td>3 years.</td>
</tr>
<tr>
<td></td>
<td>2. With less than 50 percent glycerin</td>
<td>18 months ................... do ................... 18 months.</td>
<td>18 months.</td>
</tr>
<tr>
<td></td>
<td>3. Products for which cold storage conditions are inappropriate.</td>
<td>Not applicable ................... do ...................</td>
<td>18 months (from date of manufacture), provided labeling recommends storage at 30 °C or colder.</td>
</tr>
<tr>
<td></td>
<td>4. Powders and tablets</td>
<td>do ................... do ................... 5 years (from date of manufacture), provided labeling recommends storage at 30 °C or colder.</td>
<td>5 years (from date of manufacture), provided labeling recommends storage at 30 °C or colder.</td>
</tr>
<tr>
<td></td>
<td>a. Unreconstituted</td>
<td>do ................... do ...................</td>
<td>4 years (from date of manufacture).</td>
</tr>
<tr>
<td></td>
<td>b. Reconstituted</td>
<td>do ................... do ...................</td>
<td>18 months (cannot exceed 4-year unreconstituted dating period plus an additional 12 months).</td>
</tr>
<tr>
<td>Allergenic Extracts, Alum Precipitated labeled “No U.S. Standard of Potency”, Antibody to Hepatitis B Surface Antigen</td>
<td>18 months ................... do ...................</td>
<td>18 months.</td>
<td>18 months.</td>
</tr>
<tr>
<td></td>
<td>1. Antibody to Hepatitis B Surface Antigen</td>
<td>6 months ................... do ...................</td>
<td>6 months.</td>
</tr>
<tr>
<td></td>
<td>2. Lyophilized coated red blood cells</td>
<td>do ................... do ...................</td>
<td>Do.</td>
</tr>
<tr>
<td></td>
<td>4. Powders and tablets</td>
<td>do ................... do ...................</td>
<td>Do.</td>
</tr>
<tr>
<td></td>
<td>a. Unreconstituted</td>
<td>do ................... do ...................</td>
<td>Do.</td>
</tr>
<tr>
<td></td>
<td>b. Reconstituted</td>
<td>do ................... do ...................</td>
<td>Do.</td>
</tr>
<tr>
<td></td>
<td>C</td>
<td></td>
<td>D</td>
</tr>
<tr>
<td>Product</td>
<td>A</td>
<td>B</td>
<td>C</td>
</tr>
<tr>
<td>------------------------------------------------------------------------</td>
<td>-----</td>
<td>------------------------</td>
<td>------------------------</td>
</tr>
<tr>
<td>Antivenin (Crotalidae) Polyvalent</td>
<td>......do</td>
<td>......do</td>
<td>5 years with an initial 10 percent excess of potency, provided labeling recommends storage at 37 °C or colder.</td>
</tr>
<tr>
<td>Antivenin (Latrodectus Mactans)</td>
<td>......do</td>
<td>......do</td>
<td>5 years with an initial 10 percent excess of potency. Do.</td>
</tr>
<tr>
<td>Antivenin (Micrurus fulvius)</td>
<td>......do</td>
<td>......do</td>
<td>18 months from the date of the last valid potency test.</td>
</tr>
<tr>
<td>Asparaginase</td>
<td>Not applicable</td>
<td>......do</td>
<td></td>
</tr>
<tr>
<td>BCG Vaccine</td>
<td>1 year</td>
<td>Not applicable</td>
<td>6 months.</td>
</tr>
<tr>
<td>Blood Grouping Reagents</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood Group Substance AB</td>
<td>do</td>
<td>do</td>
<td>2 years.</td>
</tr>
<tr>
<td>Blood Group Substance A</td>
<td>do</td>
<td>do</td>
<td>2 years.</td>
</tr>
<tr>
<td>Blood Group Substance B</td>
<td>do</td>
<td>do</td>
<td>Do.</td>
</tr>
<tr>
<td>Botulism Antitoxin</td>
<td>do</td>
<td>Not applicable</td>
<td>5 years with an initial 20 percent excess of potency. Do.</td>
</tr>
<tr>
<td>Cholera Vaccine</td>
<td>do</td>
<td>do</td>
<td>18 months.</td>
</tr>
<tr>
<td>Coccidioidin</td>
<td>do</td>
<td>do</td>
<td>3 years.</td>
</tr>
<tr>
<td>Collagenase</td>
<td>Not applicable</td>
<td>do</td>
<td>4 years from the date of manufacture, provided labeling recommends storage at 37 °C or colder.</td>
</tr>
<tr>
<td>Cryoprecipitated AFH</td>
<td>do</td>
<td>do</td>
<td>12 months from the date of collection of source blood, provided labeling recommends storage at −18 °C or colder.</td>
</tr>
<tr>
<td>Diphtheria Antitoxin</td>
<td>1 year</td>
<td>do</td>
<td>5 years with an initial 20 percent excess of potency. Do.</td>
</tr>
<tr>
<td>Diphtheria and Tetanus Toxoids and Pertussis Vaccine Adsorbed.</td>
<td>do</td>
<td>Not applicable</td>
<td>18 months.</td>
</tr>
<tr>
<td>Diphtheria and Tetanus Toxoids, Adsorbed.</td>
<td>do</td>
<td>do</td>
<td>2 years.</td>
</tr>
<tr>
<td>Diphtheria Toxin for Schick Test</td>
<td>do</td>
<td>do</td>
<td>1 year.</td>
</tr>
<tr>
<td>Diphtheria Toxoid</td>
<td>do</td>
<td>do</td>
<td>2 years.</td>
</tr>
<tr>
<td>Diphtheria Toxoid-Schick Test Control</td>
<td>Not applicable</td>
<td>Not applicable</td>
<td>1 year.</td>
</tr>
<tr>
<td>Factor IX Complex</td>
<td>do</td>
<td>do</td>
<td>1 year (from date of manufacture).</td>
</tr>
<tr>
<td>Fibrolysin (Human)</td>
<td>1 year</td>
<td>do</td>
<td>2 years.</td>
</tr>
<tr>
<td>Fibrolysin and Desoxyribonuclease Combined (Bovine)</td>
<td>do</td>
<td>do</td>
<td>3 years, provided labeling recommends storage at 30 °C or colder. Do.</td>
</tr>
<tr>
<td>Fibrolysin and Desoxyribonuclease Combined (Bovine) with Chloramphenicol.</td>
<td>do</td>
<td>do</td>
<td></td>
</tr>
<tr>
<td>Hepatitis B Surface Antigen:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Unlyophilized coated red blood cells</td>
<td>Not applicable</td>
<td>do</td>
<td>14 days (from date of manufacture).</td>
</tr>
<tr>
<td>2. Iodinated (125I) product</td>
<td>do</td>
<td>do</td>
<td>45 days (from date of manufacture).</td>
</tr>
<tr>
<td>3. Enzyme conjugated product</td>
<td>6 months</td>
<td>do</td>
<td>6 months.</td>
</tr>
<tr>
<td>Histoplasmin</td>
<td>1 year</td>
<td>Not applicable</td>
<td>2 years.</td>
</tr>
<tr>
<td>Immunoglobulins:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Hepatitis B Immune Globulin (Human)</td>
<td>Not applicable</td>
<td>do</td>
<td>1 year.</td>
</tr>
<tr>
<td>2. Immune Globulin (Human)</td>
<td>3 years</td>
<td>do</td>
<td>3 years.</td>
</tr>
<tr>
<td>3. Immune Globulin Intravenous (Human)</td>
<td>Not applicable</td>
<td>do</td>
<td>1 year.</td>
</tr>
<tr>
<td>5. Pertussis Immune Globulin (Human)</td>
<td>3 years</td>
<td>do</td>
<td>3 years from the date the dried or frozen bulk product is placed in final solution.</td>
</tr>
<tr>
<td>6. Rabies Immune Globulin (Human)</td>
<td>1 year</td>
<td>do</td>
<td>1 year.</td>
</tr>
<tr>
<td>7. Rh(D) Immune Globulin (Human)</td>
<td>6 months</td>
<td>do</td>
<td>6 months.</td>
</tr>
<tr>
<td>8. Tetanus Immune Globulin (Human)</td>
<td>1 year</td>
<td>do</td>
<td>3 years with an initial 10 percent excess of potency. Do.</td>
</tr>
<tr>
<td>9. Vaccinia Immune Globulin (Human)</td>
<td>3 years</td>
<td>do</td>
<td>3 years.</td>
</tr>
<tr>
<td>10. Varicella-Zoster Immune Globulin (Human).</td>
<td>Not applicable</td>
<td>do</td>
<td>1 year.</td>
</tr>
<tr>
<td>Hepatitis B Vaccine</td>
<td>2 years at 2 to 8 °C.</td>
<td>Not applicable</td>
<td>3 years.</td>
</tr>
<tr>
<td>Product</td>
<td>A</td>
<td>B</td>
<td>C</td>
</tr>
<tr>
<td>------------------------------------------------------------------------</td>
<td>---</td>
<td>---</td>
<td>-------------------------------------------------------------------</td>
</tr>
<tr>
<td>Influenza Virus Vaccine</td>
<td>1 year</td>
<td>do</td>
<td>Manufacturer's storage period 1 to 5 °C (unless otherwise stated)</td>
</tr>
<tr>
<td>Limulus Amebocyte Lysate</td>
<td>Not applicable</td>
<td>do</td>
<td>Not applicable</td>
</tr>
<tr>
<td>Measles, Mumps, and Rubella Virus Vaccine Live</td>
<td>do</td>
<td>do</td>
<td>1 year (–20 °C or colder)</td>
</tr>
<tr>
<td>Measles and Mumps Virus Vaccine Live</td>
<td>do</td>
<td>do</td>
<td>1 year (–20 °C or colder)</td>
</tr>
<tr>
<td>Measles Live and Smallpox Vaccine</td>
<td>do</td>
<td>do</td>
<td>1 year (–20 °C or colder)</td>
</tr>
<tr>
<td>Mumps Virus Vaccine Live</td>
<td>do</td>
<td>do</td>
<td>1 year (–20 °C or colder)</td>
</tr>
<tr>
<td>Meningococcal Polysaccharide Vaccine Group A:</td>
<td>1 year</td>
<td>do</td>
<td>2 years (–20 °C or colder)</td>
</tr>
<tr>
<td>Meningococcal Polysaccharide Vaccine Group C:</td>
<td>2 years</td>
<td>do</td>
<td>3 years (–20 °C or colder)</td>
</tr>
<tr>
<td>Meningococcal Polysaccharide Vaccine Groups A and C combined:</td>
<td>2 years</td>
<td>do</td>
<td>3 years (–20 °C or colder)</td>
</tr>
<tr>
<td>Meningococcal Polysaccharide Vaccine Groups A, C, Y, and W135 combined:</td>
<td>2 years</td>
<td>do</td>
<td>3 years (–20 °C or colder)</td>
</tr>
<tr>
<td>Mumps Skin Test Antigen</td>
<td>6 months</td>
<td>do</td>
<td>Not applicable</td>
</tr>
<tr>
<td>Mumps Virus Vaccine Live</td>
<td>Not applicable</td>
<td>do</td>
<td>1 year (–20 °C or colder)</td>
</tr>
<tr>
<td>Pertussis Vaccine</td>
<td>do</td>
<td>do</td>
<td>Not applicable</td>
</tr>
<tr>
<td>Pertussis Vaccine Adsorbed</td>
<td>do</td>
<td>do</td>
<td>Do.</td>
</tr>
<tr>
<td>Plague Vaccine</td>
<td>do</td>
<td>do</td>
<td>Do.</td>
</tr>
<tr>
<td>Plasma products:</td>
<td>do</td>
<td>do</td>
<td>1 year from date of collection of source blood (–18 °C or colder).</td>
</tr>
<tr>
<td>Fresh Frozen Plasma</td>
<td>Not applicable</td>
<td>do</td>
<td>(a) 26 days from date of collection of source blood (between 1 and 6 °C).</td>
</tr>
<tr>
<td>Liquid Plasma</td>
<td>do</td>
<td>do</td>
<td>(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).</td>
</tr>
<tr>
<td>Plasma</td>
<td>do</td>
<td>do</td>
<td>5 years from date of collection of source blood (–18 °C or colder).</td>
</tr>
<tr>
<td>Platelets</td>
<td>Not applicable</td>
<td>do</td>
<td>72 hours from time of collection of source blood, provided labeling recommends storage at room temperature, no warmer than 30 °C.</td>
</tr>
</tbody>
</table>

§ 610.53

21 CFR Ch. I (4–1–03 Edition)

82
### Pneumococcal Vaccine Polyvalent:

1. **Final bulk powder**: 24 months after potency assay (\( \leq -20 \) °C or colder).  
   - **Date of manufacture**: 2 years.  

2. **Final container**: 1 year.  
   - **Date of manufacture**: 1 year.  

### Poliovirus Vaccine Inactivated

1. **Frozen**: 1 year.  
   - **Condition**: \( \leq -10 \) °C or colder.  
   - **Duration**: 1 year.  

### Poliovirus Vaccine Live Oral Trivalent

1. **Frozen**: 1 year.  
   - **Condition**: \( \leq -10 \) °C or colder.  
   - **Duration**: 1 year.  
   - **Note**: Provided labeling recommends storage at a temperature which will maintain ice continuously in a solid state.  

2. **Liquid**: 30 days.  
   - **Condition**: Provided labeling recommends storage between 2 and 8 °C and container has been unopened.  

### Poliovirus Vaccine Live Oral Type I

1. **Frozen**: 1 year.  
   - **Condition**: \( \leq -10 \) °C or colder.  
   - **Duration**: 1 year.  
   - **Note**: Provided labeling recommends storage at a temperature which will maintain ice continuously in a solid state.  

2. **Liquid**: 30 days.  
   - **Condition**: Provided labeling recommends storage between 2 and 8 °C and container has been unopened.  

### Poliovirus Vaccine Live Oral Type II

1. **Frozen**: 1 year.  
   - **Condition**: \( \leq -10 \) °C or colder.  
   - **Duration**: 1 year.  
   - **Note**: Provided labeling recommends storage at a temperature which will maintain ice continuously in a solid state.  

2. **Liquid**: 30 days.  
   - **Condition**: Provided labeling recommends storage between 2 and 8 °C and container has been unopened.  

### Poliovirus Vaccine Live Oral Type III

1. **Frozen**: 1 year.  
   - **Condition**: \( \leq -10 \) °C or colder.  
   - **Duration**: 1 year.  
   - **Note**: Provided labeling recommends storage at a temperature which will maintain ice continuously in a solid state.  

2. **Liquid**: 30 days.  
   - **Condition**: 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. **Date of manufacture**: 18 months.  

### Rabies Vaccine

1. **Dried**: 2 years.  
2. **Liquid**: 6 months.  
3. **Reagent red blood cells**: Not applicable.  
4. **ACD Red Blood Cells**: 21 days from date of collection of source blood.  
5. **CPD Red Blood Cells**: 21 days from date of collection of source blood.  

---

**Notes:**

- The storage period refers to the temperature of the product when it is stored at 2 to 8 °C.
- The dating period after leaving manufacturer’s storage when stored at 2 to 8 °C is specified for each product.
- The manufacturer’s storage period is provided for conditions other than 2 to 8 °C.
- The table is structured to compare different products in terms of their storage and dating periods,

---

**Food and Drug Administration, HHS**  
§ 610.53

<table>
<thead>
<tr>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Product</strong></td>
<td><strong>Manufacturer’s storage period</strong></td>
<td><strong>Manufacturer’s storage period</strong></td>
<td><strong>Dating period after leaving manufacturer’s storage when stored at 2 to 8 °C</strong></td>
</tr>
<tr>
<td>Pneumococcal Vaccine Polyvalent:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Final bulk powder</td>
<td>do</td>
<td>24 months after potency assay (( \leq -20 ) °C or colder).</td>
<td>Not applicable.</td>
</tr>
<tr>
<td>2. Final container</td>
<td>do</td>
<td>Not applicable</td>
<td>2 years (from date of manufacture).</td>
</tr>
<tr>
<td>Poliovirus Vaccine Inactivated</td>
<td>1 year</td>
<td>do</td>
<td>1 year.</td>
</tr>
<tr>
<td>Poliovirus Vaccine Live Oral Trivalent:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Frozen</td>
<td>Not applicable</td>
<td>1 year (( \leq -10 ) °C or colder).</td>
<td>1 year, provided labeling recommends storage at a temperature which will maintain ice continuously in a solid state.</td>
</tr>
<tr>
<td>2. Liquid</td>
<td>do</td>
<td>Not applicable</td>
<td>30 days, provided labeling recommends storage between 2 and 8 °C and container has been unopened.</td>
</tr>
<tr>
<td>Poliovirus Vaccine Live Oral Type I:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Frozen</td>
<td>do</td>
<td>1 year (( \leq -10 ) °C or colder).</td>
<td>1 year, provided labeling recommends storage at a temperature which will maintain ice continuously in a solid state.</td>
</tr>
<tr>
<td>2. Liquid</td>
<td>do</td>
<td>Not applicable</td>
<td>30 days, provided labeling recommends storage between 2 and 8 °C and container has been unopened.</td>
</tr>
<tr>
<td>Poliovirus Vaccine Live Oral Type II:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Frozen</td>
<td>do</td>
<td>1 year (( \leq -10 ) °C or colder).</td>
<td>1 year, provided labeling recommends storage at a temperature which will maintain ice continuously in a solid state.</td>
</tr>
<tr>
<td>2. Liquid</td>
<td>do</td>
<td>Not applicable</td>
<td>30 days, provided labeling recommends storage between 2 and 8 °C and container has been unopened.</td>
</tr>
<tr>
<td>Poliovirus Vaccine Live Oral Type III:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Frozen</td>
<td>do</td>
<td>1 year (( \leq -10 ) °C or colder).</td>
<td>1 year, provided labeling recommends storage at a temperature which will maintain ice continuously in a solid state.</td>
</tr>
<tr>
<td>2. Liquid</td>
<td>do</td>
<td>Not applicable</td>
<td>30 days, provided labeling recommends storage between 2 and 8 °C and container has been unopened.</td>
</tr>
<tr>
<td>Poliovirus Vaccine Inactivated</td>
<td>1 year</td>
<td>do</td>
<td>1 year.</td>
</tr>
<tr>
<td>Poliovirus Vaccine Live Oral Trivalent:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Frozen</td>
<td>do</td>
<td>1 year (( \leq -10 ) °C or colder).</td>
<td>1 year, provided labeling recommends storage at a temperature which will maintain ice continuously in a solid state.</td>
</tr>
<tr>
<td>2. Liquid</td>
<td>do</td>
<td>Not applicable</td>
<td>30 days, provided labeling recommends storage between 2 and 8 °C and container has been unopened.</td>
</tr>
<tr>
<td>Poliovirus Vaccine Live Oral Type I:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Frozen</td>
<td>do</td>
<td>1 year (( \leq -10 ) °C or colder).</td>
<td>1 year, provided labeling recommends storage at a temperature which will maintain ice continuously in a solid state.</td>
</tr>
<tr>
<td>2. Liquid</td>
<td>do</td>
<td>Not applicable</td>
<td>30 days, provided labeling recommends storage between 2 and 8 °C and container has been unopened.</td>
</tr>
<tr>
<td>Poliovirus Vaccine Live Oral Type II:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Frozen</td>
<td>do</td>
<td>1 year (( \leq -10 ) °C or colder).</td>
<td>1 year, provided labeling recommends storage at a temperature which will maintain ice continuously in a solid state.</td>
</tr>
<tr>
<td>2. Liquid</td>
<td>do</td>
<td>Not applicable</td>
<td>30 days, provided labeling recommends storage between 2 and 8 °C and container has been unopened.</td>
</tr>
<tr>
<td>Poliovirus Vaccine Live Oral Type III:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Frozen</td>
<td>do</td>
<td>1 year (( \leq -10 ) °C or colder).</td>
<td>1 year, provided labeling recommends storage at a temperature which will maintain ice continuously in a solid state.</td>
</tr>
<tr>
<td>2. Liquid</td>
<td>do</td>
<td>Not applicable</td>
<td>30 days, provided labeling recommends storage between 2 and 8 °C and container has been unopened.</td>
</tr>
<tr>
<td>Polyvalent bacterial antigens with “No U.S. Standard of Potency” liquid.</td>
<td>1 year</td>
<td>do</td>
<td>18 months.</td>
</tr>
<tr>
<td>Polyvalent bacterial vaccines with “No U.S. Standard of Potency” liquid.</td>
<td>do</td>
<td>do</td>
<td>Do.</td>
</tr>
<tr>
<td>Rabies Vaccine:</td>
<td>2 years</td>
<td>6 months.</td>
<td></td>
</tr>
<tr>
<td>1. Dried</td>
<td>do</td>
<td>2 years</td>
<td>6 months.</td>
</tr>
<tr>
<td>2. Liquid</td>
<td>3 months</td>
<td>Not applicable</td>
<td>6 months.</td>
</tr>
<tr>
<td>Reagent red blood cells</td>
<td>Not applicable</td>
<td>Not applicable</td>
<td>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).</td>
</tr>
<tr>
<td>ACD Red Blood Cells</td>
<td>do</td>
<td>do</td>
<td>(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.</td>
</tr>
<tr>
<td>CPD Red Blood Cells</td>
<td>do</td>
<td>do</td>
<td>(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.</td>
</tr>
</tbody>
</table>

---

**Notes:**

- The storage period refers to the temperature of the product when it is stored at 2 to 8 °C.
- The dating period after leaving manufacturer’s storage when stored at 2 to 8 °C is specified for each product.
§610.53

<table>
<thead>
<tr>
<th>A Product</th>
<th>B Manufacturer’s storage period 1 to 5 °C (unless otherwise stated)</th>
<th>C Manufacturer’s storage period 0 °C or colder (unless otherwise stated)</th>
<th>D Dating period after leaving manufacturer’s storage when stored at 2 to 8 °C (unless otherwise stated)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPOA–1 Red Blood Cells</td>
<td>do</td>
<td>do</td>
<td>(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.</td>
</tr>
<tr>
<td>Red Blood Cells Deglycerolized</td>
<td>do</td>
<td>do</td>
<td>24 hours after removal from storage at −65 °C or colder, provided labeling recommends storage between 1 and 6 °C.</td>
</tr>
<tr>
<td>Red Blood Cells Frozen</td>
<td>do</td>
<td>do</td>
<td>3 years from date of collection of source blood, provided labeling recommends storage at −65 °C or colder.</td>
</tr>
<tr>
<td>Rubella and Mumps Virus Vaccine Live</td>
<td>do</td>
<td>1 year (−20 °C or colder).</td>
<td>1 year.</td>
</tr>
<tr>
<td>Rubella Virus Vaccine Live</td>
<td>do</td>
<td>do</td>
<td>Do.</td>
</tr>
<tr>
<td>Skin Test Antigens for Cellular Hypersensitivity.</td>
<td>6 months</td>
<td>Not applicable</td>
<td>3 months, provided labeling recommends storage at 0 °C or colder.</td>
</tr>
<tr>
<td>1. Liquid</td>
<td>Not applicable</td>
<td>9 months (−10 °C or colder, if product is maintained as glycerinated or equivalent vaccine in bulk or final containers).</td>
<td></td>
</tr>
<tr>
<td>2. Dried</td>
<td>6 months</td>
<td>Not applicable</td>
<td>18 months.</td>
</tr>
<tr>
<td>Streptokinase</td>
<td>do</td>
<td>do</td>
<td>Do.</td>
</tr>
<tr>
<td>Tetanus and Diphtheria Toxoids Adsorbed for Adult Use.</td>
<td>1 year</td>
<td>do</td>
<td>2 years.</td>
</tr>
<tr>
<td>Tetanus Antitoxin:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Liquid</td>
<td>do</td>
<td>do</td>
<td>5 years with an initial 20 percent excess or potency.</td>
</tr>
<tr>
<td>2. Dried</td>
<td>do</td>
<td>2 years</td>
<td>5 years with an initial 10 percent excess or potency.</td>
</tr>
<tr>
<td>Tetanus Toxoid</td>
<td>do</td>
<td>Not applicable</td>
<td>2 years.</td>
</tr>
<tr>
<td>Tetanus Toxoid Adsorbed</td>
<td>do</td>
<td>do</td>
<td>3 years.</td>
</tr>
<tr>
<td>Thrombin</td>
<td>do</td>
<td>2 year</td>
<td>1 year, or 6 months at 20 to 24 °C.</td>
</tr>
<tr>
<td>Thrombin Impregnated Pad</td>
<td>Not applicable</td>
<td>Not applicable</td>
<td></td>
</tr>
<tr>
<td>Tuberculin:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Purified Protein Derivative, diluted</td>
<td>6 months</td>
<td>do</td>
<td>1 year.</td>
</tr>
<tr>
<td>2. Old or Purified Protein Derivative dried on multiple puncture device.</td>
<td>1 year (not to exceed 30 °C, do not refrigerate).</td>
<td>do</td>
<td>2 years, provided labeling recommends storage at a temperature not to exceed 30 °C. Do not refrigerate.</td>
</tr>
<tr>
<td>3. Old on multiple puncture device</td>
<td>do</td>
<td>do</td>
<td>Do.</td>
</tr>
<tr>
<td>Typhoid Vaccine</td>
<td>do</td>
<td>do</td>
<td>18 months.</td>
</tr>
<tr>
<td>ACD Whole Blood</td>
<td>Not applicable</td>
<td>do</td>
<td>21 days from date of collection, provided labeling recommends storage between 1 and 6 °C.</td>
</tr>
<tr>
<td>CPD Whole Blood</td>
<td>do</td>
<td>do</td>
<td>Do.</td>
</tr>
<tr>
<td>CPOA–1 Whole Blood</td>
<td>do</td>
<td>do</td>
<td>35 days from date of collection, provided labeling recommends storage between 1 and 6 °C.</td>
</tr>
<tr>
<td>Heparin Whole Blood</td>
<td>do</td>
<td>do</td>
<td>48 hours from date of collection, provided labeling recommends storage between 1 and 6 °C.</td>
</tr>
<tr>
<td>Yellow Fever Vaccine</td>
<td>do</td>
<td>1 year (−20 °C or colder).</td>
<td>1 year, provided labeling recommends storage at 5 °C or colder.</td>
</tr>
</tbody>
</table>
§ 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;
§ 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 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.

PART 630—GENERAL REQUIREMENTS FOR BLOOD, BLOOD COMPONENTS, AND BLOOD DERIVATIVES


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
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:

1. 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;
2. Where appropriate, the types of donation of blood or blood components that the autologous donor should not donate in the future; and
3. 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.
§ 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 an 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.

Subpart A—Whole Blood

Subpart E [Reserved]

Subpart F—Cryoprecipitate

Subpart G—Source Plasma

Subpart H—Albumin (Human)

Subpart I—Plasma Protein Fraction (Human)

Subpart J—Immune Globulin (Human)

Subpart K [Reserved]

Subpart L—Alternative Procedures
§ 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 when

(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.
§ 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. Immediately after collection, unless the blood is to be used as a source for Platelets, it shall be placed in storage at a temperature between 1 and 6 °C unless it must be transported from the donor clinic to the processing
laboratory. In the latter case, the blood shall be placed in temporary storage having sufficient refrigeration capacity to cool the blood continuously toward a range between 1 and 6 °C until it arrives at the processing laboratory, where it shall be stored at a temperature between 1 and 6 °C. Blood from which Platelets is to be prepared shall be held in an environment maintained at a temperature range 20 to 24 °C until the platelets are separated. The red blood cells shall be placed in storage at a temperature between 1 and 6 °C immediately after the platelets are separated.

§ 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, this subchapter shall be used, and the technique used shall be that for which the reagent 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 D₁)” 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.

§ 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
§ 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.

§ 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.

§ 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.

§ 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.

§ 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).

§ 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 re-issued.

(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.

§ 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.
§ 640.17 Modifications for specific products.

Red Blood Cells Frozen: A cryoprophylactic 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 cryoprophylactic substance is present.


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 shall be plasma which may be obtained by whole blood collection, by plasmapheresis, or by plateletpheresis.

[40 FR 4304, Jan. 29, 1975, as amended at 47 FR 49021, Oct. 29, 1982; 50 FR 4139, Jan. 29, 1985]

§ 640.21 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). Informed consent shall be required as prescribed in §640.61.

(c) Plateletpheresis donors shall meet criteria for suitability as described in a biologics license application or a supplement to the biologics license application, and must have the written approval of the Director, Center for Biologics Evaluation and Research, Food and Drug Administration.

[40 FR 4304, Jan. 29, 1975, as amended at 49 FR 23834, June 8, 1984; 64 FR 56453, Oct. 20, 1999]

§ 640.22 Collection of source material.

(a) Whole blood used as the source of Platelets shall be collected as prescribed in §640.4.

(b) If plasmapheresis is used, the procedure for collection shall be prescribed in §§640.22, 640.64 (except paragraph (c)(3)), and 640.65.

(c) If plateletpheresis is used, the procedure for collection shall be as described in a biologics license application or a supplement to a biologics license application, and must have the written approval of the Director, Center for Biologics Evaluation and Research, Food and Drug Administration.

(d) The phlebotomy shall be performed by a single uninterrupted venipuncture with minimal damage to, and minimal manipulation of, the donor’s tissue.


§ 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.


§ 640.24 Processing.

(a) Separation of plasma and platelets and reuspension of the platelets shall be in a closed system. Platelets shall not be pooled during processing.
§ 640.25 General requirements.

(a) Storage. Immediately after re-suspension, 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 6.0 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.
§ 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
§ 640.34

venipuncture with minimal damage to and minimal manipulation of the donor’s tissue. The plasma shall be separated from the red blood cells, 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 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 “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 will show 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.


Subpart E [Reserved]
§ 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.


§ 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.


§ 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.


§ 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.


§ 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.

A U.S. Standard Antihemophilic Factor (Factor VIII) preparation may be obtained from the Center for Biologics Evaluation and Research, Food and Drug Administration, for use in the preparation of a working reference to be employed in a quality control potency test of Cryoprecipitated AHF.

§ 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.

§ 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.

§ 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;
§ 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 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.

(c) The anticoagulant solution. The anticoagulant solution shall be sterile and pyrogen-free. One of the following formulas shall be used in the indicated volumes, except that a different formula may be used for plasma for manufacture into noninjectable products if prior written approval is obtained from the Director of the Center for Biologics Evaluation and Research at the time of licensing or in the form of a supplement to the biologics license application for Source Plasma.

(1) Anticoagulant citrate dextrose solution (ACD).

<table>
<thead>
<tr>
<th>Name</th>
<th>Volume per 100 milliliters of blood</th>
<th>Constituents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tri-sodium citrate</td>
<td>22.6 grams</td>
<td>(Na$_3$C$_6$H$_5$O$_7$·2H$_2$O)</td>
</tr>
<tr>
<td>Dextrose (C$_6$H$_12$O$_6$)</td>
<td>8.0 grams</td>
<td></td>
</tr>
<tr>
<td>Water for injection (U.S.P.)</td>
<td>1,000 milliliters</td>
<td></td>
</tr>
</tbody>
</table>

(2) Anticoagulant citrate phosphate dextrose solution (CPD).

<table>
<thead>
<tr>
<th>Name</th>
<th>Volume per 100 milliliters of blood</th>
<th>Constituents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tri-sodium citrate</td>
<td>26.3 grams</td>
<td>(Na$_3$C$_6$H$_5$O$_7$·2H$_2$O)</td>
</tr>
<tr>
<td>Citric acid (C$_6$H$_8$O$_7$)</td>
<td>3.27 grams</td>
<td></td>
</tr>
<tr>
<td>Dextrose (C$_6$H$_12$O$_6$)</td>
<td>25.5 grams</td>
<td></td>
</tr>
<tr>
<td>Monobasic sodium phosphate</td>
<td>2.22 grams</td>
<td>(NaH$_2$PO$_4$·H$_2$O)</td>
</tr>
<tr>
<td>Water for injection (U.S.P.)</td>
<td>1,000 milliliters</td>
<td></td>
</tr>
</tbody>
</table>

(3) Anticoagulant sodium citrate solution.

<table>
<thead>
<tr>
<th>Name</th>
<th>Volume per 100 milliliters of blood</th>
<th>Constituents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tri-sodium citrate</td>
<td>40 grams</td>
<td>(Na$_3$C$_6$H$_5$O$_7$·2H$_2$O)</td>
</tr>
<tr>
<td>Water for injection (U.S.P.)</td>
<td>1,000 milliliters</td>
<td></td>
</tr>
</tbody>
</table>

(d) Donor identification. Each unit of blood and plasma shall be so marked or identified by number or other symbol 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.

§ 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 non-reactive 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.

§ 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.

§ 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.

§ 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.

§ 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
Food and Drug Administration, HHS

§ 640.70

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.

§ 640.70 Labeling.

(a) In addition to the labeling requirements of §610.62 of this chapter, and in lieu of the requirements in §§606.121, 610.60, and 610.61 of this chapter, the following information shall appear on the label affixed to each container of Source Plasma:

(1) The proper name of the product.

(2) The statement “Caution: For Manufacturing Use Only” for products intended for further manufacturing into injectable products, or the statement, “Caution: For Use In Manufacturing Noninjectable Products Only”, for products intended for further manufacturing into noninjectable products. The statement shall follow the proper name in the same size and type of print as the proper name. If the Source Plasma has a reactive screening test for evidence of infection due to a communicable disease agent(s) under §610.40 of this chapter, or is collected from a donor with a previous record of a reactive screening test for evidence of infection due to a communicable disease agent(s) under §610.40 of this chapter, the Source Plasma must be labeled under §610.40(h)(2)(ii)(E) of this chapter.

(3) The statement “Store at \(-20\) °C or colder”: Provided, That where plasma is intended for manufacturing into noninjectable products, this statement may be omitted if replaced by a statement of the temperature appropriate for the final product to be prepared from the plasma.

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

(5) The donor number or individual bleed number, or both. If plasma is pooled from two or more donors, either all donor numbers, all bleed numbers, or a pool number that is traceable to
§ 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 for manufacture of 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.

§ 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.

§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 §640.70(a) but excluding §640.70(a)(3), 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.


§ 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 \(-20^\circ C\) and colder than \(+10^\circ C\) 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 \(-20^\circ C\) and colder than \(-5^\circ C\) 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 \(-5^\circ C\) 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 \(-5^\circ C\) and colder than \(+10^\circ C\), 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.


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.

§ 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 one week or less 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.

§ 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.

§ 640.83 General requirements.

(a) Preservative. The final product shall not contain a preservative.
§ 640.84  
(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.  

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.


§ 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."

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.

§ 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 x 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.

§ 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.

§ 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.

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.

§ 660.1 Antibody to Hepatitis B Surface Antigen.

(a) Proper name and definition. The proper name of this product shall be Antibody to Hepatitis B Surface Antigen. The product is defined as a preparation of serum containing antibody to hepatitis B surface antigen.

(b) Source. The source of this product shall be plasma or blood, obtained aseptically from animals immunized with hepatitis B surface antigen, which have met the applicable requirements of § 600.11 of this chapter, or from human donor whose blood is positive for hepatitis B surface antigen.

[40 FR 29711, July 15, 1975]
§ 660.6 Samples; protocols; official release.

(a) Samples. (1) For the purposes of this section, a sample of product not iodinated with ¹²⁵I means a sample from each filling of each lot packaged as for distribution, including all ancillary reagents and materials; and a sample of product iodinated with ¹²⁵I means a sample from each lot of diagnostic test kits in a finished package, including all ancillary reagents and materials.

(2) Unless the Director, Center for Biologics Evaluation and Research, determines that the reliability and consistency of the finished product can be assured with a smaller quantity of sample or no sample and specifically reduces or eliminates the required quantity of sample, each manufacturer shall submit the following samples to the Director, Center for Biologics Evaluation and Research (HFB–1), 8800 Rockville Pike, Bethesda, MD 20892, within 5 working days after the manufacturer has satisfactorily completed all tests on the samples:

(i) One sample until written notification of official release is no longer required under paragraph (c)(2) of this section.

(ii) One sample at periodic intervals of 90 days, beginning after written notification of official release is no
§ 660.20 Blood Grouping Reagent.

(a) Proper name and definition. The proper name of this product shall be Blood Grouping Reagent and it shall consist of an antibody-containing fluid containing one or more of the blood grouping antibodies listed in § 660.28(d).

(b) Source. The source of this product shall be blood, plasma, serum, or protein-rich fluids, such as those derived from stable immunoglobulin-secreting cell lines maintained either in tissue cultures or in secondary hosts.

[53 FR 12764, Apr. 19, 1988, as amended at 65 FR 77499, Dec. 12, 2000]

§ 660.21 Processing.

(a) Processing method. (1) The processing method shall be one that has been shown to yield consistently a specific, potent final product, free of properties that would affect adversely the intended use of the product throughout its dating period. Stability testing shall be performed on an adequate number of representative samples of each group of products manufactured in the same fashion.

(2) Only that material that has been fully processed, thoroughly mixed in a single vessel, and filtered shall constitute a lot.

(3) A lot may be subdivided into sublots. If lots are to be subdivided, the manufacturer shall include this information in the biologics license application. The manufacturer shall describe the test specifications to verify that each sublot is identical to other sublots of the lot.
(4) Each lot of Blood Grouping Reagent shall be identified by a lot number. Each sublot shall be identified by that lot number to which a distinctive prefix or suffix shall be added. Final container and package labels shall bear the lot number and all distinctive prefixes and suffixes that have been applied to identify the sublot from which filling was accomplished.

(b) Color coding of reagents. Blood Grouping Reagents may be colored provided the added colorant does not adversely affect the safety, purity, or potency of the product and the colorant is approved by the Director, Center for Biologics Evaluation and Research (HFN–830), Food and Drug Administration, 8800 Rockville Pike, Bethesda, MD 20892.

(c) Final containers and dropper assemblies. Final containers and dropper pipettes shall be colorless and sufficiently transparent to permit observation of the contents to detect particulate matter or increased turbidity during use.

(d) Volume of final product. Each manufacturer shall identify the possible final container volumes in the biologics license application.

(e) Date of manufacture. The date of manufacture shall be the date the manufacturer begins the last entire group of potency tests.

"§ 660.25 Potency tests without reference preparations."

Products for which Reference Blood Grouping Reagents are not available shall be tested for potency by a method approved by the Director, Center for Biologics Evaluation and Research (HFN–830), Food and Drug Administration, 8800 Rockville Pike, Bethesda, MD 20892.

(a) Potency requirements. Blood Grouping Reagents recommended for the test tube methods, including the indirect antiglobulin tests, shall have the following potency titer values, unless other values are approved by the Director, Center for Biologics Evaluation and Research (HFN–830), Food and Drug Administration, 8800 Rockville Pike, Bethesda, MD 20892.

(1) For Anti-K, Anti-k, Anti-JkA, Anti-FyA, Anti-Cw, at least 1+ reaction with a 1:8 dilution of the reagent.

(2) For Anti-S, Anti-s, Anti-P, Anti-M, Anti-I, Anti-e (saline), Anti-c (saline), and Anti-A, at least 1+ reaction with a 1:4 dilution of the reagent.


(b) Products recommended for slide tests or microplate techniques. Blood Grouping Reagent recommended for slide test methods or microplate techniques shall produce clearly positive macroscopic results when both undiluted reagent and reagent diluted with an equal volume of diluent are tested by all methods recommended in the manufacturer’s package insert using red blood cells showing heterozygous or diminished expression of the corresponding antigen. The dilution shall be made with an equal volume of compatible serum or approved diluent.

(c) Products recommended for use in an automated system. The manufacturer of Blood Grouping Reagent that is recommended for use in an automated system shall demonstrate that its product when used both undiluted and diluted with an equal volume of diluent satisfactorily performs when tested with...
§ 660.26 Specificity tests and avidity tests.

Specificity and avidity tests shall be performed using test procedures approved by the Director, Center for Biologics Evaluation and Research (HFN–830), Food and Drug Administration, 8800 Rockville Pike, Bethesda, MD 20892.

[53 FR 12764, Apr. 19, 1988, as amended at 67 FR 9587, Mar. 4, 2002]

§ 660.28 Labeling.

In addition to the applicable labeling requirements of §§610.62 through 610.65 and §809.10, and in lieu of the requirements in §§610.60 and 610.61, the following requirements shall be met:

(a) Final container label—(1) Color coding. The final container label of all Blood Grouping Reagents shall be completely white, except that all or a portion of the final container label of the following Blood Grouping Reagents may be color coded with the specified color which shall be a visual match to a specific color sample designated by the Director, Center for Biologics Evaluation and Research (HFN–830), Food and Drug Administration, 8800 Rockville Pike, Bethesda, MD 20892. Printing on all final container labels shall be in solid black. A logo or company name may be placed on the final container label; however, the logo or company name shall be located along the bottom or end of the label, outside the main panel.

<table>
<thead>
<tr>
<th>Blood grouping reagent</th>
<th>Color of label paper</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-A</td>
<td>Blue.</td>
</tr>
<tr>
<td>Anti-B</td>
<td>Yellow.</td>
</tr>
<tr>
<td>Slide and rapid tube test blood grouping reagents only: Anti-C</td>
<td>Pink.</td>
</tr>
<tr>
<td></td>
<td>Gray.</td>
</tr>
<tr>
<td></td>
<td>Brown.</td>
</tr>
<tr>
<td></td>
<td>Orange.</td>
</tr>
<tr>
<td></td>
<td>Lavender.</td>
</tr>
<tr>
<td></td>
<td>Green.</td>
</tr>
</tbody>
</table>

(2) Required information. The proper name “Blood Grouping Reagent” need not appear on the final container label provided the final container is distributed in a package and the package label bears the proper name. The final container label shall bear the following information:

(i) Name of the antibody or antibodies present as set forth in paragraph (d) of this section.

(ii) Name, address (including ZIP code), and license number of the manufacturer.

(iii) Lot number, including sublot designations.

(iv) Expiration date.

(v) Source of product if other than human plasma or serum.

(vi) Test method(s) recommended.

(vii) Recommended storage temperature in degrees Celsius.

(viii) Volume of product if a liquid, or equivalent volume for a dried product if it is to be reconstituted.

(ix) If a dried product, to remind users to record the reconstitution date on the label, the statement “RECONSTITUTION DATE ______. EXPIRES 1 YEAR AFTER RECONSTITUTION DATE.”

(3) Lettering size. The type size for the specificity of the antibody designation on the labels of a final container with a capacity of less than 5 milliliters shall be not less than 12 point. The type size for the specificity of the antibody designations on the label of a container with a capacity of 5 milliliters or more shall be not less than 18 point.

(b) Package label. The following information shall appear either on the package label or on the final container label if it is visible within the package:

(1) Proper name of the product.
§ 660.32 Blood group designation for container label

<table>
<thead>
<tr>
<th>Blood Group</th>
<th>Container Label</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-A</td>
<td>Anti-Jk&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Anti-A&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Anti-Js&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Anti-A, B</td>
<td>Anti-Js&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Anti-A and B</td>
<td>Anti-K</td>
</tr>
<tr>
<td>Anti-B</td>
<td>Anti-K</td>
</tr>
<tr>
<td>Anti-C</td>
<td>Anti-Kp&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Anti-C&lt;sup&gt;w&lt;/sup&gt;</td>
<td>Anti-Le&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Anti-c</td>
<td>Anti-Le&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Anti-CD</td>
<td>Anti-Lu&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Anti-CDE</td>
<td>Anti-Lu&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Anti-DE</td>
<td>Anti-M</td>
</tr>
<tr>
<td>Anti-Di&lt;sup&gt;s&lt;/sup&gt;</td>
<td>Anti-N</td>
</tr>
<tr>
<td>Anti-E</td>
<td>Anti-P&lt;sub&gt;i&lt;/sub&gt;</td>
</tr>
<tr>
<td>Anti-e</td>
<td>Anti-S</td>
</tr>
<tr>
<td>Anti-Fy&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Anti-&lt;i&gt;z&lt;/i&gt;</td>
</tr>
<tr>
<td>Anti-Fy&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Anti-U</td>
</tr>
<tr>
<td>Anti-I</td>
<td>Anti-&lt;i&gt;Wr&lt;/i&gt;</td>
</tr>
<tr>
<td>Anti-Jk&lt;sup&gt;+&lt;/sup&gt;</td>
<td>Anti-Xg&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
</tbody>
</table>


Subpart D—Reagent Red Blood Cells

Source: 52 FR 37450, Oct. 7, 1987, unless otherwise noted.

§ 660.30 Reagent Red Blood Cells.

(a) Proper name and definition. The proper name of the product shall be Reagent Red Blood Cells, which shall consist of a preparation of human red blood cells used to detect or identify human blood-group antibodies.

(b) Source. Reagent Red Blood Cells shall be prepared from human peripheral blood meeting the criteria of §§660.31 and 660.32 of this chapter, or from umbilical cord cells which shall be collected and prepared according to the manufacturer’s biologics license application.


§ 660.31 Suitability of the donor.

Donors of peripheral blood for Reagent Red Blood Cells shall meet the criteria for donor suitability under §640.3 of this chapter, except that paragraphs (b)(5) and (6), (d), and (e) of §640.3 shall not apply.

§ 660.32 Collection of source material.

Blood for Reagent Red Blood Cells from donors of peripheral blood shall
§ 660.33 Testing of source material.

Except as provided in this section, a sample of each blood incorporated into the Reagent Red Blood Cell product shall be individually tested, with no fewer than two donor sources of each antibody specificity employed, to confirm the identification of all blood group antigens specified in the labeling as present or absent. The manufacturer shall perform at least one of the required tests for each factor. The Reagent Red Blood Cell product may be tested with a single donor source of antibody specificity if only one source of antibody is available, and the Director, Center for Biologics Evaluation and Research, has approved the use of a single donor source of antiserum. Each of these tests shall be conducted and interpreted independently, and any discrepancy between the results of these two tests shall be resolved by testing with at least one additional antiserum before concluding that the antigen is present or absent. Where fewer than three donor sources of an antibody specificity are available, test discrepancies shall be resolved in accordance with the manufacturer’s biologics license application. Group O Reagent Red Blood Cells used in the detection or identification of unexpected antibodies shall include at least the following common antigens in each lot of the product: D, C, E, c, e, K, k, Fy\textsuperscript{a}, Fy\textsuperscript{b}, Jk\textsuperscript{a}, Jk\textsuperscript{b}, Le\textsuperscript{a}, Le\textsuperscript{b}, P\textsubscript{1}, M, N, S, and s.

§ 660.34 Processing.

(a) Processing method. The processing method shall be one that has been shown to yield consistently a product that is capable of detecting, throughout the dating period, alloantibodies corresponding to all required blood group antigens specified in the labeling as present.

(b) Products prepared from pooled red blood cells. If the product is recommended for the detection of unexpected antibodies, the pool shall be prepared by combining equal amounts of cells from no more than two donors. Umbilical cord cells are exempt from this requirement. Pooled cells shall not be recommended for pretransfusion tests, done in lieu of a major cross-match, to detect unexpected antibodies in patients' samples.

(c) Absence of antibodies. Each lot of final product shall be free of demonstrable antibodies, including anti-A and anti-B, unless the package insert and container label include instructions to wash the cells before use. The final product shall also be direct antiglobulin test negative when tested with polyspecific anti-human globulin.

(d) Final container. The final containers used for each lot of product shall be clean and shall permit observation of the contents for hemolysis or a change in color. The final container label, container cap, and dropper bulb of a Reagent Red Blood Cell product may be color-coded with a visual match to a specific color approved by the Director, Center for Biologics Evaluation and Research.

(e) Date of manufacture. The date of manufacture of the product shall be the date that the blood is withdrawn from the donor or obtained from umbilical cords. The period during which the reagent red blood cell source material is kept by the manufacturer in storage in a frozen state at $-65\,^\circ C$ or colder is excluded from the dating period. If the product consists of red blood cells from two or more donors, the date of manufacture of the final product shall be the date of withdrawal of blood from the donor of the oldest constituent blood. When a product consists of more than one container, e.g., cell panel, the date of manufacture of each container of the product shall be the earliest date that blood was withdrawn from a donor for any container of the product.

§ 660.35 Retention samples. Retention samples shall be maintained as required by §660.13 of this chapter, except that samples must be retained only throughout the dating period of the product.

§ 660.35 Labeling.

In addition to the items required by §809.10 of this chapter and other applicable labeling provisions of this chapter, the following information shall be included in the labeling:

(a)(1) A logo or company name may be placed on the final container label, however, the logo or company name shall be located along the bottom or end of the label, outside of the main panel.

(2) If washing the cells is required by the manufacturer, the container label shall include appropriate instructions; if the cells should not be washed before use, e.g., if washing will adversely affect the product, the package insert shall explain.

(b) The container label of Group O cells shall state:

"FOR USE IN DETECTION OF UNEXPECTED ANTIBODIES" or "FOR USE IN IDENTIFICATION OF UNEXPECTED ANTIBODIES" or "NOT FOR USE IN DETECTION OR IDENTIFICATION OF UNEXPECTED ANTIBODIES".

(c) Except as provided in this section, the container and package labels shall state the percentage of red blood cells in the suspension either as a discrete figure with a variance of more than ±1 percentage unit or as a range the extremes of which differ by no more than 2 percentage units. If the stated red blood cell concentration is less than 2 percent, the variance shall be no more than ±0.5 percentage unit.

(d) The words "pooled cells" shall appear on the container and package labels of products prepared from pooled cells. The package label or package insert shall state that pooled cells are not recommended for pretransfusion tests, done in lieu of a major crossmatch, to detect unexpected antibodies in patients’ samples.

(e) The package insert of a pooled product intended for detection of unexpected antibodies shall identify the number of donors contributing to the pool. Products designed exclusively for ABO Serum Grouping and umbilical cord cells need not identify the number of donors in the pool.

(f) When the product is a multicontainer product, e.g., a cell panel, the container label and package label shall be assigned the same identifying lot number, and shall also bear a number or symbol to distinguish one container from another. Such number or symbol shall also appear on the antigenic constitution matrix.

(g) The package label or package insert shall state the blood group antigens that have been tested for and found present or absent on the cells of each donor, or refer to such information in an accompanying antigenic constitution matrix. Cells for ABO Serum Grouping are exempt from this requirement. The package insert or antigen constitution matrix shall list each of the antigens tested with only one source of antibody.

(h) The package label or package insert shall bear the cautionary statement: “The reactivity of the product may decrease during the dating period.”

(i) The package insert of a product intended for the detection or identification of unexpected antibodies shall note that the rate at which antigen reactivity (e.g., agglutinability) is lost is partially dependent upon individual donor characteristics that are neither controlled nor predicted by the manufacturer.

(j) The package insert shall provide adequate directions for use.

(k) The package insert shall bear the statement:

“CAUTION: ALL BLOOD PRODUCTS SHOULD BE TREATED AS POTENTIALLY INFECTIOUS. SOURCE MATERIAL FROM WHICH THIS PRODUCT WAS DERIVED WAS FOUND NEGATIVE WHEN TESTED IN ACCORDANCE WITH CURRENT FDA REQUIRED TESTS. NO KNOWN TEST METHODS CAN OFFER ASSURANCE THAT PRODUCTS DERIVED FROM HUMAN BLOOD WILL NOT TRANSMIT INFECTIOUS AGENTS.”

(l) The package insert or the antigenic constitution matrix for each lot of product shall specify the date of manufacture or the length of the dating period.

(m) Manufacturers shall identify with a permanent donor code in the product labeling each donor of peripheral blood used for detection or identification of unexpected antibodies.

§ 660.36 Samples and protocols.

(a) The following shall be submitted to the Office of Biological Product Review Sample Custodian (ATTN: HFB–215), Bldg. 29A, Rm. 1C02, Food and Drug Administration, 8800 Rockville Pike, Bethesda, MD 20892, within 30 days after each routine establishment inspection by FDA.

(1) From a lot of final product, samples from a cell panel intended for identification of unexpected antibodies. The sample shall be packaged as for distribution and shall have at least 14 days remaining in the dating period when shipped to the Center for Biologics Evaluation and Research.

(2) A protocol which shall include the following:

(i) Complete test records of at least two donors of the samples submitted, including original and confirmation phenotyping records.

(ii) Bleeding records or receipt records which indicate collection date, volume, and HBsAg test results.

(iii) Manufacturing records which document all steps involved in the preparation of the product.

(iv) Test results which verify that the final product meets specifications.

(v) Identity test results.

(b) A copy of the antigenic constitution matrix specifying the antigens present or absent shall be submitted to the Director, Center for Biologics Evaluation and Research, at the time of initial distribution of each lot of Reagent Red Blood Cells for detection or identification of unexpected antibodies. Products designed exclusively to identify Anti-A, Anti-A1, and Anti-B, as well as products composed entirely of umbilical cord cells, are excluded from this requirement.

(b) A copy of the antigenic constitution matrix specifying the antigens present or absent shall be submitted to the Director, Center for Biologics Evaluation and Research, at the time of initial distribution of each lot of Reagent Red Blood Cells for detection or identification of unexpected antibodies. Products designed exclusively to identify Anti-A, Anti-A1, and Anti-B, as well as products composed entirely of umbilical cord cells, are excluded from this requirement.

(c) Except for umbilical cord samples, whenever a new donor is used, a sample of red blood cells from each new donor used in a cell panel intended for the identification of unexpected antibodies shall be submitted by the manufacturer to the Director, Center for Biologics Evaluation and Research. The sample should contain a minimum volume of 0.5 milliliter of red blood cells.

§ 660.46 Samples; protocols; official release.

(a) Samples. (1) For the purposes of this section, a sample of product not iodinated with 125I means a sample from each filling of each lot packaged as for distribution, including all ancillary reagents and materials; and a sample of product iodinated with 125I or unlyophilized HBsAg-coated red blood cells means a sample from each lot of diagnostic test kits in a finished package, including all ancillary reagents and materials.

(2) Unless the Director, Center for Biologics Evaluation and Research, determines that the reliability and consistency of the finished product can be assured with a smaller quantity of sample or no sample and specifically reduces or eliminates the required quantity of sample, each manufacturer shall submit the following samples to the Director, Center for Biologics Evaluation and Research (HFB–1), 8800 Rockville Pike, Bethesda, MD 20892, within 5 working days after the manufacturer has satisfactorily completed all tests on the samples:

(i) One sample until written notification of official release is no longer required under paragraph (c)(2) of this section.

(ii) One sample of product at periodic intervals of 90 days, beginning after written notification of official release is no longer required under paragraph (c)(2) of this section. The sample submitted at the 90-day interval shall be from the first lot or filling, as applicable, released by the manufacturer, under the requirements of §610.1 of this chapter, after the end of the previous 90-day interval. The sample shall be identified as “surveillance sample” and shall include the date of manufacture.

§ 660.45 Labeling.

In addition to the requirements of §§610.60, 610.61, and 809.10 of this chapter, the labeling shall bear the following:

(a) The “d and y” antigen subtype and the source of the product to follow immediately the proper name on both the final container label and the package label. If the product is intended to identify antibodies to the “r and w” antigen subtype, the antigen subtype designation shall include the “r and w” antigen subtype.

(b) The name of the test method(s) recommended for use of the product on the package label and on the final container label, when capable of bearing a full label (see §610.60(a) of this chapter).

(c) A warning on the package label and on the final container label stating that the product is capable of transmitting hepatitis and should be handled accordingly.

(d) The package shall include a package insert providing (1) detailed instructions for use, (2) an adequate description of all recommended test methods, and (3) warnings as to possible hazards, including hepatitis transmitted in handling the product and any ancillary reagents and materials accompanying the product.
(iii) Samples may at any time be required to be submitted to the Director, Center for Biologics Evaluation and Research, if the Director finds that continued evaluation is necessary to ensure the potency, quality, and reliability of the product.

(b) Protocols. For each sample submitted as required in paragraph (a)(1) of this section, the manufacturer shall send a protocol that consists of a summary of the history of manufacture of the product, including all results of each test for which test results are requested by the Director, Center for Biologics Evaluation and Research. The protocols submitted with the samples at periodic intervals as provided in paragraph (a)(2)(ii) of this section shall be identified by the manufacturer as “surveillance test results.”

(c) Official release. (1) The manufacturer shall not distribute the product until written notification of official release is received from the Director, Center for Biologics Evaluation and Research, except as provided in paragraph (c)(2) of this section. Official release is required for at least five consecutive lots or fillings, as applicable, manufactured after licensure of the product.

(2) After written notification of official release is received from the Director, Center for Biologics Evaluation and Research, for at least five consecutive lots or fillings manufactured after licensure of the products, and after the manufacturer receives from the Director, Center for Biologics Evaluation and Research, written notification that official release is no longer required, subsequent lots or fillings may be released by the manufacturer under the requirements of §610.1 of this chapter.

(3) The manufacturer shall not distribute lots or fillings, as applicable, of products that require sample submission under paragraph (a)(2)(iii) of this section until written notification of official release or notification that official release is no longer required is received from the Director, Center for Biologics Evaluation and Research.

§ 660.50 Anti-Human Globulin

(a) Proper name and definition. The proper name of this product shall be Anti-Human Globulin which shall consist of one or more antiglobulin antibodies identified in §660.55(d).

(b) Source. The source of this product shall be either serum from animals immunized with one or more human serum globulins or protein-rich fluids derived from stable immunoglobulin-secreting cell lines maintained either in tissue cultures or in secondary hosts.

§ 660.51 Processing.

(a) Processing method. (1) The processing method shall be one that has been shown to yield consistently a specific, potent final product, free of properties that would adversely affect the product for its intended use throughout its dating period.

(2) Anti-IgG, –C3d (polyspecific) reagents and anti-IgG products may be colored green.

(3) Only that material which has been fully processed, thoroughly mixed in a single vessel, and filtered shall constitute a lot. Each lot shall be identified by a lot number.

(4) A lot may be subdivided into sublots which shall be identified by the lot number to which has been added a distinctive prefix or suffix. If lots are to be subdivided, the manufacturer shall include this information in the license application. The manufacturer shall describe the test specifications to verify that each sublot is identical to other sublots of the lot.

(b) Final containers and dropper assemblies. (1) Final containers and dropper assemblies shall be clean.

(2) Final containers and dropper pipettes shall be colorless and sufficiently transparent to permit observation of the contents for presence of particulate matter or increased turbidity.

(c) Date of manufacture. The date of manufacture shall be the date the manufacturer begins the last entire group of potency tests.


§ 660.52 Reference preparations.

Reference Anti-Human Globulin preparations shall be obtained from the Center for Biologics Evaluation and Research (HFB–221), Food and Drug Administration, 8800 Rockville Pike, Bethesda, MD 20892, and shall be used as described in the accompanying package insert for determining the potency of Anti-Human Globulin.


§ 660.53 Controls for serological procedures.

Red blood cells sensitized with complement shall be tested with appropriate positive and negative control antisera. All tests shall be performed in accordance with serological testing procedures approved by the Director, Center for Biologics Evaluation and Research (HFB–1), Food and Drug Administration, 8800 Rockville Pike, Bethesda, MD 20892.


§ 660.54 Potency tests, specificity tests, tests for heterospecific antibodies, and additional tests for nonspecific properties.

The following tests shall be performed using test procedures approved by the Director, Center for Biologics Evaluation and Research (HFB–1), Food and Drug Administration, 8800 Rockville Pike, Bethesda, MD 20892:

(a) Potency tests for determining anti-IgG and anti-complement activity.

(b) Specificity tests, tests for heterospecific antibodies, and additional tests for nonspecific properties.


§ 660.55 Labeling.

In addition to the applicable labeling requirements of §§610.62 through 610.65 and §809.10 of this chapter, and in lieu of the requirements in §§610.60 and 610.61 of this chapter, the following requirements shall be met:

(a) Final container label—(1) Color coding. The main panel of the final container label of all Anti-IgG, –C3d (polyspecific) reagents shall be white or colorless and printing shall be solid dark contrasting lettering. The main panel of the final container label of all other Anti-Human Globulin reagents shall be black with solid white lettering. A logo or company name may be placed on the final container label, however, the logo or company name shall be located along the bottom or end of the label, outside of the main panel.

(2) Required information. The proper name “Anti-Human Globulin” need not appear on the final container label provided the final container is distributed in a package and the package label bears the proper name. The final container label shall bear the following information:

(i) Name of the antibody or antibodies present as set forth in paragraph (d) of this section. Anti-Human Globulin may contain one or more antibodies to either immunoglobulins or complement components but the name of each significant antibody must appear on the final container label (e.g., anti-C3b, –C3d, –C4d). The final container labels of polyspecific Anti-Human Globulin are not required to identify antibody specificities other than anti-IgG and anti-C3d but the reactivity of the Anti-Human Globulin shall be accurately described in the package insert.

(ii) Name, address, and license number of the manufacturer.

(iii) Lot number, including any sublot designations.

(iv) Expiration date.
(v) Source of the product.
(vi) Recommended storage temperature in degrees Celsius.
(vii) Volume of product.
(viii) Appropriate cautionary statement if the Anti-Human Globulin is not polyspecific. For example, “DOES NOT CONTAIN ANTIBODIES TO IMMUNOGLOBULINS” or “DOES NOT CONTAIN ANTIBODIES TO COMPLEMENT COMPONENTS.”
(ix) If the final container is not enclosed in a package, all items required for a package label shall appear on the container label.

(3) **Lettering size.** The type size for the designation of the specific antibody on the label of a final container shall be not less than 12 point, unless otherwise approved by the Director, Center for Biologics Evaluation and Research (HFB–1). The prefix anti- and other parts of the name such as polyspecific may appear in smaller type.

(4) **Visual inspection.** When the label has been affixed to the final container, a sufficient area of the container shall remain uncovered for its full length or for no less than 5 millimeters of the lower circumference to permit inspection of the contents.

(b) **Package label.** The following items shall appear either on the package label or on the final container label if see-through packaging is used:

(1) Proper name of the product, and the name of the antibody or antibodies as listed in paragraph (d) of this section.
(2) Name, address (including zip code), and license number of the manufacturer.
(3) Lot number, including any sublot designations.
(4) Expiration date.
(5) Preservative(s) used and its concentration.
(6) Number of containers, if more than one.
(7) Recommended storage temperature in degrees Celsius.
(8) Source of the product.
(9) Reference to enclosed package insert.
(10) The statement: “For In Vitro Diagnostic Use.”
(11) The statement: “Meets FDA Potency Requirements.”
(12) A statement of an observable indication of an alteration of the product, e.g., turbidity, color change, precipitate, that may indicate possible deterioration of the product.

(13) **Appropriate cautions.**

(c) **Package insert.** Each final container of Anti-Human Globulin shall be accompanied by a package insert meeting the requirements of §809.10 of this chapter. If two or more final containers requiring identical package inserts are placed in a single package, only one package insert per package is required.

(d) **Names of antibodies.**

<table>
<thead>
<tr>
<th>Antibody designation on container label</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-IgG, C3b; Polyspecific .............</td>
<td>Contains anti-IgG and anti-C3b (may contain other anticomplement and anti-immunoglobulin antibodies).</td>
</tr>
<tr>
<td>Anti-IgG ..................................</td>
<td>Contains anti-IgG with no anti-complement activity (not necessarily gamma chain specific).</td>
</tr>
<tr>
<td>Anti-IgG, heavy chains .................</td>
<td>Contains only antibodies reactive against human gamma chains.</td>
</tr>
<tr>
<td>Anti-C3b .................</td>
<td>Contains only C3b antibodies with no anti-immunoglobulin activity. <strong>Note:</strong> The antibody produced in response to immunization is usually directed against the antigenic determinant which is located in the C3c subunit; some persons have called this antibody “anti-C3c.” In product labeling, this antibody should be designated anti-C3b.</td>
</tr>
<tr>
<td>Anti-C3d .................</td>
<td>Contains only C3d antibodies with no anti-immunoglobulin activity.</td>
</tr>
<tr>
<td>Anti-C4b .................</td>
<td>Contains only C4b antibodies with no anti-immunoglobulin activity.</td>
</tr>
<tr>
<td>Anti-C4d .................</td>
<td>Contains only C4d antibodies with no anti-immunoglobulin activity.</td>
</tr>
</tbody>
</table>

**Anti-Human Globulin preparations may contain one or more of the antibody specificities listed in this paragraph as described in paragraph (a)(2)(i) of this section.**


**PART 680—ADDITIONAL STANDARDS FOR MISCELLANEOUS PRODUCTS**

Sec. 680.1 Allergenic Products.
680.2 Manufacture of Allergenic Products.
680.3 Tests.

§ 680.1 Allergenic Products.

(a) Definition. Allergenic Products are products that are administered to man for the diagnosis, prevention or treatment of allergies.

(b) Source materials—

(1) Criteria for source material. Only specifically identified allergenic source materials that contain no more than a total of 1.0 percent of detectable foreign materials shall be used in the manufacture of Allergenic Products, except that this requirement shall not apply to molds and animals described under paragraphs (b) (2) and (3) of this section, respectively. Source materials such as pelts, feathers, hairs, and danders shall be collected in a manner that will minimize contamination of the source material.

(2) Molds. (i) Molds (excluding rusts and smuts) used as source material in the manufacture of Allergenic Products shall meet the requirements of §610.18 of this chapter and §680.2 (a) and (b).

(ii) Mold cultures shall be free of contaminating materials (including microorganisms) prior to harvest, and care shall be taken to minimize contamination during harvest and subsequent processing.

(iii) Mold manufacturers shall maintain written standard operating procedures, developed by a qualified individual, that will ensure the identity of the seed culture, prescribe adequate processing of the mold, and specify the acceptable limits and kinds of contamination. These limits shall be based on results of appropriate tests performed by the manufacturer on at least three consecutive lots of a mold that is a representative species of mold subject to the standard operating procedures. The tests shall be performed at each manufacturing step during and subsequent to harvest, as specified in the standard operating procedures. Before use of the mold as a source material for Allergenic Products, in accordance with 21 CFR 601.2, the standard operating procedures and test data from the three representative lots described above shall be submitted to and approved by the Director, Center for Biologics Evaluation and Research (HFB–1).

(3) Mammals and birds—(i) Care of animals. Animals intended as a source material for Allergenic Products shall be maintained by competent personnel in facilities or designated areas that will ensure adequate care. Competent veterinary care shall be provided as needed.

(ii) Health of animals. Only animals in good health and free from detectable skin diseases shall be used as a source material for Allergenic Products. The determination of good health prior to collection of the source material shall be made by a licensed veterinarian or a competent individual under the supervision and instruction of a licensed veterinarian provided that the licensed veterinarian certifies in writing that the individual is capable of determining the good health of the animals.

(iii) Immunization against tetanus. Animals of the equine genus intended as a source material for Allergenic Products shall be treated to maintain immunity to tetanus.

(iv) 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 as source material in the manufacture of allergenic Products, the manufacturer shall immediately notify the Director, Center for Biologics Evaluation and Research (HFB–1).

(v) Dead animals. Dead animals may be used as source material in the manufacture of Allergenic Products: Provided, That (a) the carcasses shall be frozen or kept cold until the allergen can be collected, or shall be stored under other acceptable conditions so that the postmortem decomposition processes do not adversely affect the allergen, and (b) when alive, the animal...
§ 680.2 Manufacture of Allergenic Products.

(a) Extraneous allergenic substances. All manufacturing steps shall be performed so as to ensure that the product will contain only the allergenic and other substances intended to be included in the final product.

(b) Cultures derived from microorganisms. Culture media into which organisms are inoculated for the manufacture of Allergenic Products shall contain no allergenic substances other than those necessary as a growth requirement. Neither horse protein nor any allergenic derivative of horse protein shall be used in culture media.

(c) Liquid products for oral administration. Liquid products intended for oral administration that are filled in multiple dose final containers shall contain a preservative in a concentration adequate to inhibit microbial growth.

(d) Residual pyridine. Products for which pyridine is used in manufacturing shall have no more residual pyridine in the final product than 25 micrograms per milliliter.

(e) [Reserved]

(f) Records. A record of the history of the manufacture or propagation of each lot of source material intended for manufacture of final Allergenic Products shall be available at the establishment of the manufacturer of the source material, as required by §211.188 of this chapter. A summary of the history of the manufacture or propagation of the source material shall be available at the establishment of the manufacturer of the final product.


§ 680.3 Tests.

(a) Identity. When a specific identity test meeting the provisions of §610.14 of this chapter cannot be performed, the manufacture of each lot shall be separated from the manufacture of other products in a manner that will preclude adulteration, and records made in the course of manufacture shall be in sufficient detail to verify the identity of the product.

(b) Safety. A safety test shall be performed on the contents of a final container of each lot of each product as prescribed in §610.11 of this chapter, except for the following:

(1) For lots consisting of no more than 20 final containers or 20 sets of individual dilutions, or where the final container contains no more than one intended human dose, the safety test need not be performed on the contents.
Food and Drug Administration, HHS

§ 680.3

of a final container provided the safety test is performed on each lot of stock concentrate and on each lot of diluent contained in the final product. Only stock concentrates and diluents which have passed the general safety test shall be kept in the work areas used for the manufacture of Allergenic Products. A stock concentrate is an extract derived from a single allergenic source and used in the manufacture of more than one lot of product, and from which final dilutions or mixtures, are prepared directly.

(2) For powders for scratch tests, a sample shall be suspended in a suitable diluent and injected into each animal, and the sample size shall be the single human dose recommended.

(c) Sterility. A sterility test shall be performed on each lot of each Allergenic Product as prescribed in §610.12 of this chapter, with the following exceptions:

(1) When bulk material is not prepared, the sterility test prescribed for bulk material shall be performed on each container of each stock concentrate at the time a stock concentrate is prepared, and the test sample shall be no less than 1 ml. from each stock concentrate container.

(2) For lots consisting of no more than 5 final containers, the final container test shall be performed in accordance with §610.12(g)(6) of this chapter using the sample therein prescribed or using a sample of no less than 0.25 ml. of product from each final container, divided in approximately equal proportions for testing in Fluid Thioglycollate and Soybean-Casein Digest Media. The test sample in the later alternative method may be an overfill in the final container.

(3) For products prepared in sets of individual dilution series, a test sample of 0.25 ml. shall be taken from a final container of each dilution, which samples may be pooled and one half of the pooled material used for the test with Fluid Thioglycollate Medium and one half used for the test with Soybean-Casein Digest Medium.

(4) Tablets and capsules need not be tested for sterility provided aseptic techniques are employed in their manufacture.

(d) [Reserved]

(e) Potency. The potency of each lot of each Allergenic Product shall be determined as prescribed in §610.10 of this chapter. Except as provided in this section, the potency test methods shall measure the allergenic activity of the product. Until manufacturers are notified by the Director, Center for Biologics Evaluation and Research, of the existence of a potency test that measures the allergenic activity of an allergenic product, manufacturers may continue to use unstandardized potency designations.

(f) Records. The records related to the testing requirements of this section shall be prepared and maintained as required by §§211.165, 211.167, 211.188, and 211.194 of this chapter.