code of federal regulations

Food and Drugs

21

PARTS 600 TO 799

Revised as of April 1, 1996

CONTAINING
A CODIFICATION OF DOCUMENTS
OF GENERAL APPLICABILITY
AND FUTURE EFFECT

AS OF APRIL 1, 1996

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Cite this Code: CFR

To cite the regulations in this volume use title, part and section number. Thus, 21 CFR 600.3 *refers to title 21, part 600, section 3.*

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Each volume of the Code is revised at least once each calendar year and issued on a quarterly basis approximately as follows:

Title 1 through Title 16.....as of January 1
Title 17 through Title 27.....as of April 1
Title 28 through Title 41.....as of July 1
Title 42 through Title 50.....as of October 1

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RICHARD L. CLAYPOOLE,
Director,
Office of the Federal Register.

April 1, 1996.

THIS TITLE

Title 21—FOOD AND DRUGS is composed of nine volumes. The parts in these volumes are arranged in the following order: Parts 1–99, 100–169, 170–199, 200–299, 300–499, 500–599, 600–799, 800–1299 and 1300–end. The first eight volumes, containing parts 1–1299, comprise Chapter I—Food and Drug Administration, Department of Health and Human Services. The ninth volume, containing part 1300 to end, includes Chapter II—Drug Enforcement Administration, Department of Justice, and Chapter III—Office of National Drug Control Policy. The contents of these volumes represent all current regulations codified under this title of the CFR as of April 1, 1996.

The Table of Exempt Prescription Products to part 1308 appears in the volume containing part 1300–end.

Redesignation tables for Chapter I—Food and Drug Administration appear in the Finding Aids section for the volumes containing parts 170–199 and 500–599.

For this volume, Ruth Reedy Green was Chief Editor. The Code of Federal Regulations publication program is under the direction of Frances D. McDonald, assisted by Alomha S. Morris.

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Title 21—Food and Drugs

(This book contains parts 600 to 799)

CROSS REFERENCES: Food Safety and Inspection Service, Department of Agriculture: See Meat and Poultry Inspection, 9 CFR Chapter III.

Federal Trade Commission: See Commercial Practices, 16 CFR Chapter I.

U.S. Customs Service, Department of the Treasury: See Customs Duties, 19 CFR Chapter I.

Internal Revenue Service, Department of the Treasury: See Internal Revenue, 26 CFR Chapter I.

Bureau of Alcohol, Tobacco, and Firearms, Department of the Treasury: See Alcohol, Tobacco Products and Firearms, 27 CFR Chapter I.

CHAPTER I—FOOD AND DRUG ADMINISTRATION, DEPARTMENT OF HEALTH AND HUMAN SERVICES—(Continued)

(Parts 600–799)

SUBCHAPTER F—BIOLOGICS

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SUBCHAPTER F—BIOLOGICS

PART 600—BIOLOGICAL PRODUCTS: GENERAL

Subpart A—General Provisions

Subpart B—Establishment Standards

Subpart C—Establishment Inspection

Subpart D—Reporting of Adverse Experiences

AUTHORITY: Secs. 201, 501, 502, 503, 505, 510, 519, 701, 704 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, 351, 352, 353, 355, 360, 360i, 371, 374); secs. 215, 351, 352, 353, 361, 2125 of the Public Health Service Act (42 U.S.C. 216, 262, 263, 263a, 264, 300aa-25).

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

Subpart A—General Provisions

§ 600.3 Definitions.

As used in this subchapter:

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

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

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

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

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

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

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

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

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

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

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

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

(5) A product is analogous:

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

(ii) To a therapeutic serum, if composed of whole blood or plasma or

containing some organic constituent or product other than a hormone or an amino acid, derived from whole blood, plasma, or serum.

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

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

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

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

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

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

(n) The word *standards* means specifications and procedures applicable to an establishment or to the manufacture or release of products, which are prescribed in this subchapter and which are 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.

(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* 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.

[38 FR 32048, Nov. 20, 1973, as amended at 40 FR 31313, July 25, 1975; 55 FR 11014, Mar. 26, 1990]

Subpart B—Establishment Standards

§ 600.10 Personnel.

(a) *Responsible head.* A person shall be designated as the responsible head who shall exercise control of the establishment in all matters relating to compliance with the provisions of this subchapter, with authority to represent the manufacturer in all pertinent matters with the Center for Biologics Evaluation and Research, and with authority to enforce or to direct the enforcement of discipline and the performance of assigned functions by employees engaged in the manufacture of products. The responsible head shall have an understanding of the scientific principles and the techniques involved in the manufacture of products. The responsible head shall have the responsibility for the training of employees in manufacturing methods and for their being informed concerning the application of the pertinent provisions of this subchapter to their respective functions.

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

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

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

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

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

contact with other animals during the same working day.

[38 FR 32048, Nov. 20, 1973, as amended at 49 FR 23833, June 8, 1984; 55 FR 11014, Mar. 26, 1990]

§ 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.

(5) [Reserved]

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

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

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

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

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

the lot number, and the filling identification.

[38 FR 32048, Nov. 20, 1973, as amended at 41 FR 10428, Mar. 11, 1976; 49 FR 23833, June 8, 1984; 55 FR 11013, Mar. 26, 1990]

§ 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.

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

§ 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.

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

§ 600.14 Reporting of errors.

(a) The Director, Office of Compliance, Center for Biologics Evaluation and Research (HFB–100), 8800 Rockville Pike, Bethesda, MD 20892, shall be notified promptly of errors or accidents in the manufacture of products that may affect the safety, purity, or potency of any product.

(b) Manufacturers of licensed in vitro diagnostic products, and manufacturers of unlicensed in vitro diagnostic products which are required to be registered under part 607 of this chapter, shall notify the Director in accordance with paragraph (a) of this section. Manufacturers of other in vitro diagnostic products which are required to be registered under part 807 of this chapter, shall report in accordance with part 803 of this chapter.

[38 FR 32048, Nov. 20, 1973, as amended at 49 FR 23833, June 8, 1984; 49 FR 36348, Sept. 14, 1984; 55 FR 11014, Mar. 26, 1990]

§ 600.15 Temperatures during shipment.

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

(a) *Products.*

Product	Temperature
Cryoprecipitated AHF	−18 °C or colder.
Measles and Rubella Virus Vaccine Live.	10 °C or colder.
Measles Live and Smallpox Vaccine.	Do.
Measles, Mumps, and Rubella Virus Vaccine Live.	Do.
Measles and Mumps Virus Vaccine Live.	Do.
Measles Virus Vaccine Live	Do.
Mumps Virus Vaccine Live	Do.
Fresh Frozen Plasma	−18 °C or colder.
Liquid Plasma	1° to 10°C.
Plasma	−18 °C or colder.
Platelet Rich Plasma	Between 1 and 10 °C if the label indicates storage between 1 and 6 °C, or all reasonable methods to maintain the temperature as close as possible to a range between 20 and 24 °C, if the label indicates storage between 20 and 24 °C.
Platelets	Between 1 and 10 °C if the label indicates storage between 1 and 6 °C, or all reasonable methods to maintain the temperature as close as possible to a range between 20 to 24 °C, if the label indicates storage between 20 and 24 °C.
Poliovirus Vaccine Live Oral Trivalent.	0 °C or colder.
Poliovirus Vaccine Live Oral Type I.	Do.
Poliovirus Vaccine Live Oral Type II.	Do.
Poliovirus Vaccine Live Oral Type III.	Do.
Red Blood Cells (liquid product).	Between 1 and 10 °C.
Red Blood Cells Frozen	−65 °C or colder.
Rubella and Mumps Virus Vaccine Live.	10 °C or colder.
Rubella Virus Vaccine Live	Do.
Smallpox Vaccine (Liquid Product).	0 °C or colder.
Source Plasma	−5 °C or colder.
Source Plasma Liquid	10 °C or colder.
Whole Blood	Blood that is transported from the collecting facility to the processing facility shall be transported in an environment capable of continuously cooling the blood toward a temperature range of 1 ° to 10 °C, or at a temperature as close as possible to 20 ° to 24 °C for a period not to exceed 6 hours. Blood transported from the storage facility shall be placed in an appropriate environment to maintain a temperature range between 1 to 10 °C during shipment.
Yellow Fever Vaccine	0 °C or colder.

(b) *Exemptions.* Exemptions or modifications shall be made only upon written approval, in the form of a

supplement of the product license, issued by the Director, Center for Biologics Evaluation and Research.

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

Subpart C—Establishment Inspection

§ 600.20 Inspectors.

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

[38 FR 32048, Nov. 20, 1973]

§ 600.21 Time of inspection.

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

[38 FR 32048, Nov. 20, 1973, as amended at 48 FR 26314, June 7, 1983]

§ 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.

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

Subpart D—Reporting of Adverse Experiences

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

§ 600.80 Postmarketing reporting of adverse experiences.

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

Adverse experience means 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 for this purpose has the same meaning as defined in § 606.3(c) of this chapter.

Increased frequency means an increase in the rate of occurrence of a particular adverse biological product experience, e.g., an increased number of reports of a particular adverse biological product experience after appropriate adjustment for biological product exposure.

Serious means an adverse experience associated with the use of a biological product that is fatal or life-threatening, is permanently disabling, requires inpatient hospitalization, or is a congenital anomaly, cancer, or overdose.

Unexpected means an adverse biological product experience that is not listed in the current labeling for the product and includes an event that may be symptomatically and pathophysiologically related to an event listed in the labeling, but differs from the event because of greater severity or specificity. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the labeling only referred to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the labeling only listed cerebral vascular accidents.

(b) *Review of adverse experiences.* Any person having a product 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.

(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) *Fifteen-day Alert reports.* (i) The licensed manufacturer shall report each adverse experience that is both serious and unexpected, regardless of source, as soon as possible but in any case within 15 working days of initial receipt of the information. These reports are required to be submitted, for nonvaccine biological products, on a form designated by FDA or a suitable format containing all of the data elements in the FDA designated reporting form, and, for vaccines on a VAERS form. The licensed manufacturer shall promptly investigate all adverse experiences that are the subject of these 15-day Alert reports and shall submit followup reports within 15 working days of receipt of new information or as requested by FDA. If additional information is not obtainable, a followup report may be required that describes briefly the steps taken to seek additional information and the reasons why it could not be obtained. These 15-day Alert reports and followups to them are required to be submitted under separate cover and may not be included, except for summary or tabular purposes, in a periodic report.

(ii) The licensed manufacturer shall review periodically (at least as often as the periodic reporting cycle) the frequency of reports of adverse biological product experiences that are both serious and expected and reports of therapeutic failure (lack of effect), regardless of source, and report any significant increase in frequency as soon as possible but in any case within 15 working days of determining that a significant increase in frequency exists. Upon written notice, FDA may require that licensed manufacturers

review the frequency of reports of serious, expected adverse biological product experiences at intervals different than the periodic reporting cycle. Reports of a significant increase in frequency are required to be submitted in narrative form (including the time period on which the increased frequency is based, the method of analysis, and the interpretation of the results), rather than using the form designated by FDA. Fifteen-day Alert reports based on increased frequency are required to be submitted under separate cover and may not be included, except for summary purposes, in a periodic report.

(iii) The requirements of paragraphs (c)(1)(i) and (c)(1)(ii) of this section, concerning the submission of Fifteen-day Alert reports, shall also apply to any person other than the licensed manufacturer of the final product 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. In order to avoid unnecessary duplication in the initial and followup submission of reports to FDA, the obligations of a manufacturer other than the licensed manufacturer, may be met by submitting all reports to the licensed manufacturer of the final product. If a manufacturer other than the licensed manufacturer elects to submit reports to the licensed manufacturer rather than to FDA, it shall submit each report to the licensed manufacturer within 3 working days of its receipt, and the licensed manufacturer shall then comply with the requirements of this section. Under this circumstance, the manufacturer 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,

(B) Date the report was received by the manufacturer,

(C) Date the report was submitted to the licensed manufacturer,

(D) Name and address of the licensed manufacturer.

(iv) 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 product 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 product license) and each annual report within 60 days of the anniversary date of the issuance of the product license. Upon written notice, FDA may extend or reestablish the requirement that a licensed manufacturer submit quarterly reports, or require that the licensed manufacturer submit reports under this section at different times than those stated. Followup information to adverse experiences submitted in a periodic report may be submitted in the next periodic report.

(ii) Each periodic report shall contain:

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

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

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

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

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

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

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

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

(f) *Reporting forms.* (1) Except as provided in paragraphs (c)(1)(ii), and (f)(3) of this section, the licensed manufacturer shall complete the reporting form designated by FDA (FDA–3500A, or, for vaccines, a VAERS form) for each report of an adverse experience.

(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 experiences that occurred in clinical trials if they were previously submitted in the product 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 license for the product listed first in the report.

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

hospitals, and geographical identifiers in adverse experience reports are not releasable to the public under FDA's public information regulations in part 20 this of chapter. For vaccine adverse experience reports, these data will become part of the CDC Privacy Act System 09–20–0136, ''Epidemiologic Studies and Surveillance of Disease Problems.'' Information identifying the person who received the vaccine or that person's legal representative will not be made available to the public, but may be available to the vaccinee or legal representative.

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

(j) *Guideline.* FDA has prepared a guideline for the submission of reports of adverse experiences and suggested followup investigation of reports.

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

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

(1) Whole blood or components of whole blood.

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

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

§ 600.81 Distribution reports.

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

§ 600.90 Waivers.

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

(1) An explanation why the licensed manufacturer's compliance with the

requirement is unnecessary or cannot be achieved,

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

(3) Other information justifying a waiver.

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

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

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

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

PART 601—LICENSING

Subpart A—General Provisions

Subpart B—Establishment Licensing

Subpart C—Product Licensing

Subpart D—Licensing of Foreign Establishments and Products

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

Subpart F—Confidentiality of Information

AUTHORITY: Secs. 201, 501, 502, 503, 505, 510, 513–516, 518–520, 701, 704, 721, 801 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, 351, 352, 353, 355, 360, 360c–360f, 360h–360j, 371, 374, 379e, 381); secs. 215, 301, 351, 352 of the Public Health Service Act (42 U.S.C. 216, 241, 262, 263); secs. 2–12 of the Fair Packaging and Labeling Act (15 U.S.C. 1451–1461).

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

§ 601.1 Two forms of licenses.

There shall be two forms of licenses: establishment and product.

§ 601.2 Applications for establishment and product licenses; procedures for filing.

(a) *General.* To obtain a license for any establishment or product, the manufacturer shall make application to the Director, Center for Biologics Evaluation and Research, on forms prescribed for such purposes, and in the case of an application for a product license, shall submit data derived from

nonclinical laboratory and clinical studies which demonstrate that the manufactured product meets prescribed standards of safety, purity, and potency; with respect to each nonclinical laboratory study, either a statement that the study was conducted in compliance with the requirements set forth in part 58 of this chapter, or, if the study was not conducted in compliance with such regulations, a brief statement of the reason for the noncompliance; statements regarding each clinical investigation involving human subjects contained in the application, that it either was conducted in compliance with the requirements for institutional review set forth in part 56 of this chapter or was not subject to such requirements in accordance with §56.104 or §56.105, and was conducted in compliance with requirements for informed consent set forth in part 50 of this chapter; a full description of manufacturing methods; data establishing stability of the product through the dating period; sample(s) representative of the product to be sold, bartered, or exchanged or offered, sent, carried or brought for sale, barter, or exchange; summaries of results of tests performed on the lot(s) represented by the submitted sample(s); and specimens of the labels, enclosures, and containers proposed to be used for the product. An application for 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 §25.24 of this chapter or an environmental assessment under §25.31 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.

(b) *Radioactive biological products.* In lieu of submitting an establishment and product license for the manufacture of a radioactive biological product, as defined in §600.3(ee) of this chapter, the manufacturer of such a product shall submit a new drug application to the Director, Division of Medical Imaging, Surgical, and Dental Products (HFD–160), Center for Drug Evaluation and Research, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, consistent with the procedures set forth in §314.50 of this chapter. For such products, the approval of the new drug application will be in lieu of issuing a product and an establishment license. Compliance with the provisions of part 314 of this chapter shall be deemed to constitute compliance with the provisions of Subchapter F of this chapter unless the Commissioner makes a determination that a particular regulation from Subchapter F shall be applicable to radioactive drugs containing a biological product, e.g., §610.2 of this chapter.

[40 FR 31313, July 25, 1975, as amended at 46 FR 8955, Jan. 27, 1981; 47 FR 6618, Feb. 16, 1982; 49 FR 23833, June 8, 1984; 50 FR 7518, Feb. 22, 1985; 50 FR 16669, Apr. 26, 1985; 55 FR 11013 and 11014, Mar. 26, 1990]

§601.3 License forms.

(a) *Establishment license.* The establishment license form shall be prescribed by the Director, Center for Biologics Evaluation and Research and shall include:

(1) The name and address of the manufacturer.

(2) The name and address of the establishment.

(3) The names and addresses of all locations of the establishment.

(4) The license number.

(5) The date of issuance.

(b) *Product license.* The product license form shall be prescribed by the Director, Center for Biologics Evaluation and Research and shall include:

(1) The name and address of the manufacturer.

(2) The name and address of the establishment.

(3) The name and address of each location at which the product is manufactured.

(4) The license number of the establishment.

(5) The proper name of the product, with additional specifications, if any, which may be approved or required for additional labeling purposes.

[38 FR 32052, Nov. 20, 1973, as amended at 49 FR 23833, June 8, 1984; 55 FR 11013, Mar. 26, 1990]

§ 601.4 Issuance and denial of license.

(a) An establishment or product license shall be issued upon a determination by the Director, Center for Biologics Evaluation and Research that the establishment or the product, as the case may be, meets the applicable standards established in this chapter. Licenses shall be valid until suspended or revoked.

(b) If the Commissioner determines that the establishment or product does not meet the standards established in this chapter, he shall deny the application and inform the applicant of the grounds for, and of an opportunity for a hearing on, his decision. If the applicant so requests, the Commissioner shall issue a notice of opportunity for hearing on the matter pursuant to § 12.21(b) of this chapter.

[42 FR 4718, Jan. 25, 1977, as amended at 42 FR 15676, Mar. 22, 1977; 42 FR 19142, Apr. 12, 1977; 49 FR 23833, June 8, 1984; 55 FR 11013, Mar. 26, 1990]

§ 601.5 Revocation of license.

(a) An establishment or product license shall be revoked upon application of the manufacturer giving notice of intention to discontinue the manufacture of all products 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) If the Commissioner finds that (1) 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, (2) manufacturing of products or of a product has been discontinued to an extent that a meaningful inspection or evaluation cannot be made, (3) the manufacturer has failed to report a change as required by § 601.12, (4) the establishment or any location thereof, or the product for which the license has been issued, fails to conform to the applicable standards established in the license and in this chapter designed to ensure the continued safety, purity, and potency of the manufactured product, (5) the establishment or the manufacturing methods have been so changed as to require a new showing that the establishment or product meets the standards established in this chapter in order to protect the public health, or (6) the licensed product is not safe and effective for all of its intended uses or is misbranded with respect to any such use, he shall notify the licensee of his intention to revoke the license, setting forth the grounds for, and offering an opportunity for a hearing on, the proposed revocation. Except as provided in § 601.6 or in cases involving willfulness, the notification required in this paragraph shall provide a reasonable period for the licensee 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 licensee does not waive the opportunity for a hearing, the Commissioner shall issue a notice of opportunity for hearing on the matter pursuant to § 12.21(b) of this chapter.

[42 FR 4718, Jan. 25, 1977, as amended at 42 FR 15676, Mar. 22, 1977; 42 FR 19143, Apr. 12, 1977; 49 FR 23833, June 8, 1984]

§ 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, he may notify the licensee that his license for the establishment or the product is suspended and require that the licensee (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 pursuant to the provisions of § 601.5(b) to revoke the license, or (2) if the licensee agrees, hold revocation in abeyance pending resolution of the matters involved.

[42 FR 4718, Jan. 25, 1977 as amended at 49 FR 23833, June 8, 1984; 55 FR 11013, Mar. 26, 1990]

§ 601.7 Procedure for hearings.

(a) A notice of opportunity for hearing, notice of appearance and request

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

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

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

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

§ 601.8 Publication of revocation.

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 standards.* An establishment or product license, previously suspended or revoked, may be reissued or reinstated upon a showing of compliance with required standards 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.* An establishment or product license, excluding a location or locations that fail to comply with required standards, may be issued without further application and concurrently with the suspension or revocation of the license for noncompliance at the excluded location or locations.

[42 FR 4718, Jan. 25, 1977, as amemded at 49 FR 23833, June 8, 1984; 55 FR 11013, Mar. 26, 1990]

Subpart B—Establishment Licensing

§ 601.10 Establishment licenses; issuance and conditions.

(a) *Inspection—compliance with standards.* An establishment license shall be issued only after inspection of the establishment and upon a determination that the establishment complies with the applicable standards prescribed in the regulations in this subchapter.

(b) *Availability of product; simultaneous request for and issuance of product license.* No establishment license shall be issued unless (1) a product intended for sale, barter or exchange or intended to be offered, sent, carried or brought for sale, barter or exchange is available for examination, (2) such product is available for inspection during all phases of manufacture and (3) a product license is requested and issued simultaneously with the establishment license.

(c) *One establishment license to cover all locations.* One establishment license shall be issued to cover all locations meeting the establishment standards.

§ 601.12 Changes to be reported.

(a) *General.* Important proposed changes in location, equipment, management and responsible personnel, or in manufacturing methods and labeling, of any product for which a license is in effect or for which an application for license is pending, shall be reported to the Director, Center for Biologics Evaluation and Research, by the manufacturer, and unless in case of an emergency, not less than 30 days in advance of the time such changes are intended to be made.

(b) *Manufacturing methods and labeling.* Proposed changes in manufacturing methods and labeling may not become effective until notification of acceptance is received from the Director, Center for Biologics Evaluation and Research.

[38 FR 32052, Nov. 20, 1973. Redesignated and amended at 42 FR 4718, Jan. 25, 1977; 49 FR 23833, June 8, 1984; 55 FR 11013, Mar. 26, 1990]

Subpart C—Product Licensing

§ 601.20 Product licenses; issuance and conditions.

(a) *Examination—compliance with standards.* A product license shall be issued only upon examination of the product and upon a determination that the product complies with the standards prescribed in the regulations in this subchapter: *Provided,* That no product license shall be issued except upon a determination that the establishment complies with the establishment standards prescribed in the regulations contained in this subchapter, applicable to the manufacture of such product.

(b) *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 Commissioner of Food and Drugs, would impair the assurances of continued safety, purity and potency as provided by the regulations contained in this subchapter.

§ 601.21 Products under development.

A biological product undergoing development, but not yet ready for a product 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 sale, barter, or exchange, except as provided in section 505(i) of the Federal Food, Drug, and Cosmetic Act, as amended, and the regulations thereunder (21 CFR part 312).

[45 FR 73923, Nov. 7, 1980, as amended at 55 FR 11014, Mar. 26, 1990]

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

Licenses issued to a manufacturer for an establishment shall authorize persons other than such manufacturer to conduct at places other than such establishment 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 he finds upon application of such manufacturer, that (a) 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 (b) such manufacturer has established with respect to such persons and places such procedures, inspections, tests or other arrangements as will assure 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 §§ 601.1 to 601.6, 601.9, 601.10, 601.20, 601.21, 601.30 to 601.33, and §§610.60 to 610.65 of this chapter. Failure of such manufacturer to maintain such procedures, inspections, tests, or other arrangements, or failure of any person conducting such partial manufacturing to comply with applicable regulations shall constitute a ground for suspension or revocation of the authority conferred pursuant to this section on the same basis as provided in §§ 601.6 to 601.8 with respect to the suspension and the revocation of licenses.

[42 FR 4718, Jan. 25, 1977]

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

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

(a) *Advisory review panels.* The Commissioner of Food and Drugs shall appoint advisory review panels (1) to evaluate the safety and effectiveness of biological products for which a license has been issued pursuant to section 351 of the Public Health Service Act, (2) to review the labeling of such biological products, and (3) to advise him on

which of the biological products under review are safe, effective, and not misbranded. An advisory review panel shall be established for each designated category of biological product. The members of a panel shall be qualified experts, appointed by the Commissioner, and shall include persons from lists submitted by organizations representing professional, consumer, and industry interests. Such persons shall represent a wide divergence of responsible medical and scientific opinion. The Commissioner shall designate the chairman of each panel, and summary minutes of all meetings shall be made.

(b) *Request for data and views.* (1) The Commissioner of Food and Drugs will publish a notice in the FEDERAL REGISTER requesting interested persons to submit, for review and evaluation by an advisory review panel, published and unpublished data and information pertinent to a designated category of biological products.

(2) Data and information submitted pursuant to a published notice, and falling within the confidentiality provisions of 18 U.S.C. 1905, 5 U.S.C. 552(b), or 21 U.S.C. 331(j), shall be handled by the advisory review panel and the Food and Drug Administration as confidential until publication of a proposed evaluation of the biologics under review and the full report or reports of the panel. Thirty days thereafter such data and information shall be made publicly available and may be viewed at the Dockets Management Branch of the Food and Drug Administration, except to the extent that the person submitting it demonstrates that it still falls within the confidentiality provisions of one or more of those statutes.

(3) To be considered, 12 copies of the submission on any marketed biological product within the class shall be submitted, preferably bound, indexed, and on standard sized paper, approximately 8½ × 11 inches. The time allotted for submissions will be 60 days, unless otherwise indicated in the specific notice requesting data and views for a particular category of biological products. When requested, abbreviated submissions should be sent. All submissions shall be in the following format, indicating ''none'' or ''not applicable'' where appropriate, unless changed in the FEDERAL REGISTER notice:

BIOLOGICAL PRODUCTS REVIEW INFORMATION

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

II. Representative advertising used during the past 5 years.

III. The complete quantitative composition of the biological product.

IV. Animal safety data.

A. Individual active components.

1. Controlled studies.

2. Partially controlled or uncontrolled studies.

B. Combinations of the individual active components.

1. Controlled studies.

2. Partially controlled or uncontrolled studies.

C. Finished biological product.

1. Controlled studies.

2. Partially controlled or uncontrolled studies.

V. Human safety data.

A. Individual active components.

1. Controlled studies.

2. Partially controlled or uncontrolled studies.

3. Documented case reports.

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

5. Pertinent medical and scientific literature.

B. Combinations of the individual active components.

1. Controlled studies.

2. Partially controlled or uncontrolled studies.

3. Documented case reports.

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

5. Pertinent medical and scientific literature.

C. Finished biological product.

1. Controlled studies.

2. Partially controlled or uncontrolled studies.

3. Documented case reports.

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

5. Pertinent medical and scientific literature.

VI. Efficacy data.

A. Individual active components.

1. Controlled studies.

2. Partially controlled or uncontrolled studies.

3. Documented case reports.

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

5. Pertinent medical and scientific literature.

B. Combinations of the individual active components.

1. Controlled studies.

2. Partially controlled or uncontrolled studies.

3. Documented case reports.

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

5. Pertinent medical and scientific literature.

C. Finished biological product.

1. Controlled studies.

2. Partially controlled or uncontrolled studies.

3. Documented case reports.

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

5. Pertinent medical and scientific literature.

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

VIII. If the submission is by a licensee, a statement signed by the responsible head (as defined in § 600.10 of this chapter) of the licensee shall be included, stating that to the best of his 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 licensee, 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 information, favorable and unfavorable, available to him pertinent to an evaluation of the safety, effectiveness, and labeling of the product.

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

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

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

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

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

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

(2) Effectiveness means a reasonable expectation that, in a significant proportion of the target population, the pharmacological or other effect of the biological product, when used under adequate directions, for use and warnings against unsafe use, will serve a clinically significant function in the diagnosis, cure, mitigation, treatment, or prevention of disease in man. Proof of effectiveness shall consist of controlled clinical investigations as

defined in § 314.126 of this chapter, unless this requirement is waived on the basis of a showing that it is not reasonably applicable to the biological product or essential to the validity of the investigation, and that an alternative method of investigation is adequate to substantiate effectiveness. Alternate methods, such as serological response evaluation in clinical studies and appropriate animal and other laboratory assay evaluations may be adequate to substantiate effectiveness where a previously accepted correlation between data generated in this way and clinical effectiveness already exists. Investigations may be corroborated by partially controlled or uncontrolled studies, documented clinical studies by qualified experts, and reports of significant human experience during marketing. Isolated case reports, random experience, and reports lacking the details which permit scientific evaluation will not be considered.

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

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

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

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

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

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

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

(f) *Proposed order.* After reviewing the conclusions and recommendations of the advisory review panel, the

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

Commissioner of Food and Drugs shall publish in the FEDERAL REGISTER a proposed order containing:

(1) A statement designating the biological products in the category under review that are determined by the Commissioner of Food and Drugs to be safe and effective and not misbranded. This statement may include any condition relating to active components, labeling, tests required prior to release of lots, product standards, or other conditions necessary or appropriate for their safety and effectiveness, and may propose corresponding amendments in other regulations under this subchapter F.

(2) A statement designating the biological products in the category under review that are determined by the Commissioner of Food and Drugs to be unsafe or ineffective, or to be misbranded, together with the reasons therefor. All licenses for such products shall be proposed to be revoked.

(3) A statement designating the biological products not included in either of the above two statements on the basis of the Commissioner of Food and Drugs determination that the available data are insufficient to classify such biological products under either paragraph (f) (1) or (2) of this section. Licenses for such products may be proposed to be revoked or to remain in effect on an interim basis. Where the Commissioner determines that the potential benefits outweigh the potential risks, the proposed order shall provide that the product license for any biological product, falling within this paragraph will not be revoked but will remain in effect on an interim basis while the data necessary to support its continued marketing are being obtained for evaluation by the Food and Drug Administration. The tests necessary to resolve whatever safety or effectiveness questions exist shall be described.[2]

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

(4) The full report or reports of the panel to the Commissioner of Food and Drugs.

The summary minutes of the panel meeting or meetings shall be made available to interested persons upon request. Any interested person may within 90 days after publication of the proposed order in the FEDERAL REGISTER, file with the Hearing Clerk of the Food and Drug Administration written comments in quintuplicate. Comments may be accompanied by a memorandum or brief in support thereof. All comments may be reviewed at the office of the Dockets Management Branch during regular working hours, Monday through Friday.

(g) *Final order.* After reviewing the comments, the Commissioner of Food and Drugs shall publish in the FEDERAL REGISTER a final order on the matters covered in the proposed order. The final order shall become effective as specified in the order.

(h) [Reserved]

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

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

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

This regulation establishes procedures for the reclassification of all biological products that have been classified into Category IIIA. A Category IIIA biological product is one for which an advisory review panel has recommended under § 601.25(e)(3), the Commissioner of Food and Drugs (Commissioner) has proposed under § 601.25(f)(3), or the Commissioner has finally

decided under § 601.25(g) that available data are insufficient to determine whether the product license should be revoked or affirmed and which may be marketed pending the completion of further testing. All of these Category IIIA products will either be reclassified into Category I (safe, effective, and not misbranded) or Category II (unsafe, ineffective, or misbranded) in accordance with the procedures set forth below.

(a) *Advisory review panels.* The Commissioner will appoint advisory review panels and use existing advisory review panels to (1) evaluate the safety and effectiveness of all Category IIIA biological products; (2) review the labeling of such products; and (3) advise the Commissioner on which Category IIIA biological products are safe, effective, and not misbranded. These advisory review panels will be established in accordance with procedures set forth in § 601.25(a).

(b) *Deliberations of advisory review panels.* The deliberations of advisory review panels will be conducted in accordance with § 601.25(d).

(c) *Advisory review panel report to the Commissioner.* An advisory review panel shall submit to the Commissioner a report containing the panel's conclusions and recommendations with respect to the biological products falling within the category of products reviewed by the panel. The panel report shall include:

(1) A statement designating the biological products in the category under review in accordance with either § 601.25(e)(1) or § 601.25(e)(2).

(2) A statement identifying those biological products designated under § 601.25(e)(2) that the panel recommends should be designated as safe and presumptively effective and should remain on the market pending completion of further testing because there is a compelling medical need and no suitable alternative therapeutic, prophylactic, or diagnostic agent that is available in sufficient quantities to meet current medical needs. For the products or categories of products so recommended, the report shall include: (i) A description and evaluation of the available evidence concerning effectiveness and an explanation why the evidence shows that the product has any benefit; and (ii) a description of the alternative therapeutic, prophylactic, or diagnostic agents considered and a statement of why such alternatives are not suitable. In making this recommendation the panel shall also take into account the seriousness of the condition intended to be treated, prevented, or diagnosed by the product, the risks involved in the continued use of the product, and the likelihood that, based upon existing data, the effectiveness of the product can eventually be established by further testing and new test development. The report shall also recommend with as much specificity as possible the type of further testing required and the time period within which it might reasonably be concluded.

(d) *Proposed order.* After reviewing the conclusions and recommendations of the advisory review panels, the Commissioner shall publish in the FEDERAL REGISTER a proposed order containing:

(1) A statement designating the biological products in the category under review in accordance with either § 601.25(e)(1) or 601.25(e)(2);

(2) A notice of availability of the full panel report or reports. The full panel report or reports shall be made publicly available at the time of publication of the proposed order.

(3) A proposal to accept or reject the findings of the advisory review panel required by § 601.26(c)(2)(i) and (ii).

(4) A statement identifying those biological products that the Commissioner proposes should be designated as safe and presumptively effective under § 601.26(c)(2) and should be permitted to remain on the market pending completion of further testing because there is a compelling medical need and no suitable alternative therapeutic, prophylactic, or diagnostic agent for the product that is available in sufficient quantities to meet current medical needs. In making this proposal, the Commissioner shall take into account the seriousness of the condition to be treated, prevented, or diagnosed by the product, the risks involved in the continued use of the product, and the likelihood that, based upon existing data, the effectiveness of the product can eventually be established by further testing.

(e) *Final order.* After reviewing the comments on the proposed order, the Commissioner shall publish in the FEDERAL REGISTER a final order on the matters covered in the proposed order. Where the Commissioner determines that there is a compelling medical need and no suitable alternative therapeutic, prophylactic, or diagnostic agent for any biological product that is available in sufficient quantities to meet current medical needs, the final order shall provide that the product license for that biological product will not be revoked, but will remain in effect on an interim basis while the data necessary to support its continued marketing are being obtained for evaluation by the Food and Drug Administration. The final order shall describe the tests necessary to resolve whatever effectiveness questions exist.

(f) *Additional studies and labeling.* (1) Within 60 days following publication of the final order, each licensee for a biological product designated as requiring further study to justify continued marketing on an interim basis, pursuant to 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 licensee 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 product 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 product 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 product license or licenses involved. In making this review the Commissioner may again consult the advisory review panel which prepared the report on the product, or other advisory committees, professional organizations, or experts. The Commissioner shall take such action by notice published in the FEDERAL REGISTER.

(4) Labeling and promotional material for those biological products requiring additional studies shall bear a box statement in the following format:

> Based on a review by the (*insert name of appropriate advisory review panel*) and other information, the Food and Drug Administration has directed that further investigation be conducted before this product is conclusively determined to be effective for labeled indication(s).

(5) A written informed consent shall be obtained from participants in any additional studies required under paragraph (f)(1) of this section, explaining the nature of the product and the investigation. The explanation shall consist of such disclosure and be made so that intelligent and informed consent be given and that a clear opportunity to refuse is presented.

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

(h) [Reserved]

(i) *Institutional review and informed consent.* Information and data submitted under this section after July 27, 1981, shall include statements regarding each clinical investigation involving human subjects, that it was conducted in compliance with the requirements for informed consent under part

50 of this chapter. Such a study is also subject to the requirements for institutional review under part 56 of this chapter, unless exempt under § 56.104 or § 56.105.

[47 FR 44071, Oct. 5, 1982]

Subpart D—Licensing of Foreign Establishments and Products

§ 601.30 Licenses required; products for controlled investigation only.

Any biological or trivalent organic arsenical manufactured in any foreign country and intended for sale, barter, or exchange shall be refused entry by collectors of customs unless manufactured in an establishment holding an unsuspended and unrevoked establishment license and license for the product. Unlicensed products that are not imported for sale, barter, or exchange and that are intended solely for purposes of controlled investigation are admissible only if the investigation is conducted in accordance with section 505 of the Federal Food, Drug, and Cosmetic Act and the requirements set forth in parts 50, 56 unless exempted under § 56.104 as granted a waiver under § 56.105, parts 58 and 312 of this chapter.

[46 FR 8956, Jan. 27, 1981]

§ 601.31 Procedure.

Except as otherwise provided in this subchapter, licenses for foreign establishments and products shall be issued, suspended, and revoked in the same manner as licenses for domestic establishments and products. Each foreign establishment holding a license and sending, carrying, or bringing any licensed product into any State or possession for sale, barter, or exchange shall file with the Director, Center for Biologics Evaluation and Research, the name and address of each person to whom such a product is thus sent, carried, or brought. Foreign licensees shall notify each person in the United States to whom such a product is thus sent, carried, or brought, to keep such records of distribution as are required of domestic licensed establishments. Failure to give such notice to maintain records shall constitute ground for revocation of license.

[38 FR 32052, Nov. 20, 1973, as amended at 49 FR 23833, June 8, 1984; 55 FR 11013, Mar. 26, 1990]

§ 601.32 Form of license.

Licenses for establishments located in foreign countries shall be in form similar to that for domestic establishments except that they shall authorize manufacture for sending, carrying, or bringing for sale, barter or exchange from the foreign country designated in the license into any State or possession of the United States and shall specify that it is issued upon the condition that the licensee will permit the inspection during all reasonable hours of the establishment by any officer, agent, or employee of the Department of Health and Human Services authorized by the Secretary for such purpose.

§ 601.33 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.

[38 FR 32052, Nov. 20, 1973, as amended at 49 FR 23833, June 8, 1984; 55 FR 11013, Mar. 26, 1990]

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 reporting applicable to all approved biological products.

§ 601.45 Promotional materials.

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

§ 601.46 Termination of requirements.

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

Subpart F—Confidentiality of Information

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

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

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

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

[39 FR 44656, Dec. 24, 1974]

§ 601.51 Confidentiality of data and information in applications for establishment and product 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 an establishment or product 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 product license has been sent to the applicant, 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 has been issued.

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

(d) If the existence of a biological product file has been publicly disclosed or acknowledged before a license has been issued, no data or information contained in the file is available for public disclosure before such license is issued, but the Commissioner may, in his discretion, disclose a summary of such selected portions of the safety and effectiveness data as are appropriate for public consideration of a specific pending issue, e.g., at an open session of a Food and Drug Administration advisory committee or pursuant to an exchange of important regulatory information with a foreign government.

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

(1) All safety and effectiveness data and information.

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

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

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

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

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

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

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

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

(8) All records showing the testing of and action on a particular lot by the Food and Drug Administration.

(f) The following data and information in a biological product file are not available for public disclosure unless they have been previously disclosed to the public as defined in §20.81 of this chapter or they relate to a product or ingredient that has been abandoned and they no longer represent a trade secret or confidential commercial or financial information as defined in §20.61 of this chapter:

(1) Manufacturing methods or processes, including quality control procedures.

(2) Production, sales, distribution, and similar data and information, except that any compilation of such data and information aggregated and prepared in a way that does not reveal data or information which is not available for public disclosure under this provision is available for public disclosure.

(3) Quantitative or semiquantitative formulas.

(g) For purposes of this regulation, safety and effectiveness data include

all studies and tests of a biological product on animals and humans and all studies and tests on the drug for identity, stability, purity, potency, and bioavailability.

[39 FR 44656, Dec. 24, 1974, as amended at 42 FR 15676, Mar. 22, 1977; 49 FR 23833, June 8, 1984; 55 FR 11013, Mar. 26, 1990]

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

Subpart A—General Provisions

Subpart B—Organization and Personnel

Subpart C—Plant and Facilities

Subpart D—Equipment

Subpart E—[Reserved]

Subpart F—Production and Process Controls

Subpart G—Finished Product Control

Subpart H—Laboratory Controls

Subpart I—Records and Reports

AUTHORITY: Secs. 201, 301, 501, 502, 505, 510, 520, 701, 704 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, 331, 351, 352, 355, 360, 360j, 371, 374); secs. 215, 351, 353, 361 of the Public Health Service Act (42 U.S.C. 216, 262, 263a, 264).

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

Subpart A—General Provisions

§ 606.3 Definitions.

As used in this part:

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

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

(c) *Component* means that part of a single-donor unit of 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. This process may be immediately repeated, once.

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

(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 in vitro serological tests performed on donor and recipient blood samples to establish the serological matching of a

donor's blood or blood components with that of a potential recipient.

Subpart B—Organization and Personnel

§ 606.20 Personnel.

(a) A blood establishment shall be under the direction of a designated, qualified person who shall exercise control of the establishment in all matters relating to compliance with the provisions of this subchapter. This person shall also have the authority to represent the establishment in all pertinent matters with the Center for Biologics Evaluation and Research and to enforce, or direct the enforcement of, discipline and the performance of assigned functions by employees engaged in the collection, processing, compatibility testing, storage and distribution of blood and blood components. The designated director shall have an understanding of the scientific principles and techniques involved in the manufacture of blood products and shall have the responsibility for ensuring that employees are adequately trained in standard operating procedures and that they are aware of the application of the pertinent provisions of this chapter to their respective functions.

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

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

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

Subpart C—Plant and Facilities

§ 606.40 Facilities.

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

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

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

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

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

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

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

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

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

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

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

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

(c) Provide adequate, clean, and convenient handwashing facilities for personnel, and adequate, clean, and convenient toilet facilities for donors and personnel. Drains shall be of adequate size and, where connected directly to a

sewer, shall be equipped with traps to prevent back-siphonage.

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

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

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

Subpart D—Equipment

§ 606.60 Equipment.

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

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

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

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

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

§ 606.65 Supplies and reagents.

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

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

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

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

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

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

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

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

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

Subpart E—[Reserved]

Subpart F—Production and Process Controls

§ 606.100 Standard operating procedures.

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

(b) Written standard operating procedures shall be maintained and shall include all steps to be followed in the collection, processing, compatibility testing, storage and distribution of blood and blood components for homologous transfusion, autologous transfusion and further manufacturing purposes. Such procedures shall be available to the personnel for use in the areas where the procedures are performed, unless this is impractical. 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 processing, including testing for hepatitis B surface antigen as prescribed in § 610.40 of this chapter.

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

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

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

(1) American Association of Blood Banks.

(2) American National Red Cross.

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

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

§ 606.110 Plateletpheresis, leukapheresis, and plasmapheresis.

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

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

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

Subpart G—Finished Product Control

§ 606.120 Labeling, general requirements.

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

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

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

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

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

(c) All labeling shall be clear and legible.

[50 FR 35469, Aug. 30, 1985]

§ 606.121 Container label.

(a) The container label requirements are designed to facilitate the use of a uniform container label for blood and blood components (except Source Plasma) by all blood establishments. Single copies of an FDA guideline entitled ''Guideline for the Uniform Labeling of Blood and Blood Components'' are available upon request (under Docket No. 80N–0120) from the Dockets Management Branch (HFA–305), Food and Drug Administration, Rm. 1–23, 12420 Parklawn Dr., Rockville, MD 20857 (copies of the guideline are available also from the American Blood Commission, 1901 North Ft. Myer Drive, Suite 300, Arlington, VA 22209).

(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.

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

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

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

(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) ''Caution: Federal law prohibits dispensing without prescription.''

(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^u 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^u 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.

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

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

(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 and expressd as follows: (*a*) ACD, (*b*) CPD, (*c*) Heparin, (*d*) CPDA–1, (*e*) CP2D, or by other nomenclature approved for use by the Director, Office of Biologics Research and Review (HFN–800), Center for Drugs and Biologics.

(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: ''Caution: For Manufacturing Use Only''; or ''Caution: For Use in Manufacturing Noninjectable Products Only'', as applicable.

(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 351 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) As required under § 610.40 of this chapter, labels for blood and blood components that are reactive for Hepatitis B Surface Antigen, but that are intended for further manufacturing, shall state conspicuously that the material is reactive when tested for hepatitis B surface antigen and may transmit viral hepatitis or, as applicable, that blood was collected from a donor known to be reactive for hepatitis B surface antigen and is presumed to be infectious, although confirmatory hepatitis testing has not been done.

(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, 610.45, and 640.5 (a), (b), or (c) of this chapter completed before shipment.

(3) Indication of any tests prescribed under §§ 610.40, 610.45, 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 (i)(1), (2), and (3) of this section.

[50 FR 35469, Aug. 30, 1985, as amended at 53 FR 116, Jan. 5, 1988; 55 FR 11014, Mar. 26, 1990; 57 FR 10814, Mar. 31, 1992; 59 FR 23636, May 6, 1994]

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 hepatitis is present. Careful donor selection and available laboratory tests do not eliminate the hazard.''

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

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

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

(j) [Reserved]

(k) For Red Blood Cells, the 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.

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

(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 37 °C.

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

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

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

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

[50 FR 35470, Aug. 30, 1985, as amended at 53 FR 116, Jan. 5, 1988]

EFFECTIVE DATE NOTE: The information collection requirements contained in § 606.122 will not become effective until OMB approval has been obtained. FDA will publish a notice of OMB approval in the FEDERAL REGISTER.

Subpart H—Laboratory Controls

§ 606.140 Laboratory controls.

Laboratory control procedures shall include:

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

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

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

§ 606.151 Compatibility testing.

Standard operating procedures for compatibility testing shall include the following:

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

(b) The use of fresh recipient serum samples less than 48 hours old for all pretransfusion testing.

(c) The testing of the donor's cells with the recipient's serum (major crossmatch) by a method that will demonstrate agglutinating, coating and hemolytic antibodies, which shall include the antiglobulin method.

(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 transfusions in life-threatening emergencies. Records of all such incidents shall be maintained, including complete documentation justifying the emergency action, which shall be signed by the physician requesting the procedure.

Subpart I—Records and Reports

§ 606.160 Records.

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

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

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

(1) Donor records:

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

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

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

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

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

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

(2) Processing records:

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

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

(iii) Separation and pooling of recovered plasma.

(iv) Centrifugation and pooling of source plasma.

(v) Labeling, including initials of person(s) responsible.

(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) Errors and accidents.

(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, Center for Biologics Evaluation and Research, shall be notified by telephone or telegraph as soon as possible; a written report of the investigation shall be submitted to the Director, Office of Compliance, 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.

(Information collection requirements approved by the Office of Management and Budget under control number 0910–0116)

[40 FR 53532, Nov. 18, 1975, as amended at 49 FR 23833, June 8, 1984; 50 FR 35471, Aug. 30, 1985; 55 FR 11014, Mar. 26, 1990]

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

Subpart A—General Provisions

Sec.

Subpart B—Procedures for Domestic Blood Product Establishments

AUTHORITY: Secs. 201, 301, 501, 502, 505, 510, 701, 704 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, 331, 351, 352, 355, 360, 371, 374); secs. 215, 351 of the Public Health Service Act (42 U.S.C. 216, 262).

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

Subpart A—General Provisions

§ 607.3 Definitions.

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

(b) *Blood and blood product* means a drug which consists of human whole blood, plasma, or serum or any product derived from human whole blood, plasma or serum, hereinafter referred to as ''blood product.''

(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 pursuant to 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 domestic establishments within the same parent, subsidiary, and/or affiliate company.

(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.

[40 FR 52788, Nov. 12, 1975, as amended at 55 FR 11014, Mar. 26, 1990]

§ 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 (HFB–240), 8800 Rockville Pike, Bethesda, MD 20892 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 (HFB–240), 8800 Rockville Pike, Bethesda, MD 20892.

[40 FR 52788, Nov. 12, 1975, as amended at 49 FR 23833, June 8, 1984; 55 FR 11014, Mar. 26, 1990]

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 607, that engage in the manufacture of blood products are required to register and to submit a list of every blood product in commercial distribution (except that 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), 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 an establishment license application to manufacture blood products are required to register before the establishment 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.

§ 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)) for which a license is required, registration shall follow within 5 days after the submission of an establishment and product 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.

§ 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 (HFB–240), 8800 Rockville Pike, Bethesda, MD 20892, 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 pursuant to § 607.35. The completed form shall be mailed to the above 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. In lieu of Form FD–2830, tapes for computer input may be submitted if equivalent

in all elements of information as specified in Form FD–2830. All formats proposed for such use will require initial review and approval by the Office of Compliance, Center for Biologics Evaluation and Research, Food and Drug Administration.

[40 FR 52788, Nov. 12, 1975, as amended at 49 FR 23833, June 8, 1984; 55 FR 11014, Mar. 26, 1990]

§ 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 ZIP 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 every blood product establishment within the parent company at which it is manufactured.

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

§ 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 FD–2830 (Blood Establishment Registration and Product Listing) as 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 reason for discontinuance of distribution be included with this information.

(3) A list of each blood product for which a notice of discontinuance was submitted pursuant to paragraph (a)(2) of this section and for which commercial distribution has been resumed, including for each blood product so listed

the identity by established name as defined in section 502(e) of the act and by any proprietary name, the date of resumption, and any other information required by § 607.25(b) not previously submitted.

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

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

§ 607.31 Additional blood product listing information.

(a) In addition to the information routinely required by §§ 607.25 and 607.30, the Commissioner 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 Commissioner for good cause, a copy of all advertisements.

(2) For a particular blood product so listed, upon a finding by the Commissioner 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 Commissioner that it is necessary to carry out the purposes of the act, a list of each listed blood product containing a particular ingredient.

(b) It is requested but not required that information concerning the quantity of blood product distributed be submitted in conjunction with the annual registration in the format prescribed in a section of Form FD–2831 (Blood Establishment Resource Summary), for each blood product currently listed.

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

(a) The Commissioner 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 only to the location shown for the registering establishment. A permanent registration number will be assigned to each blood product establishment registered in accordance with these regulations.

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

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

[40 FR 52788, Nov. 12, 1975, as amended at 49 FR 23833, June 8, 1984]

§ 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 pursuant to section 510(f) of the act, at the Department of Health and Human Services, Food and Drug Administration, Office of Compliance, Center for Biologics Evaluation and Research (HFB–100), 8800 Rockville Pike, Bethesda, MD 20892. In addition, there will be available for inspection at each of the Food and Drug Administration district offices the same information 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 a registered establishment will be provided. The following information submitted pursuant to the blood product listing requirements is illustrative of the type of information that will be available for public disclosure when it is compiled:

(1) A list of all blood products.

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

(3) A list of blood products discontinued.

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

(b) Requests for information regarding blood establishment registrations and blood product listings should be directed to the Department of Health and Human Services, Food and Drug Administration, Office of Compliance, Center for Biologics Evaluation and Research (HFB–100), 8800 Rockville Pike, Bethesda, MD 20892.

[40 FR 52788, Nov. 12, 1975, as amended at 49 FR 23833, June 8, 1984; 55 FR 11014, Mar. 26, 1990]

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

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

Subpart C—Procedures for Foreign Blood Product Establishments

§ 607.40 Blood product listing requirements for foreign blood product establishments.

(a) Every foreign establishment shall comply with the blood product listing requirements contained in Subpart B of this part, unless exempt under Subpart D of this part, whether or not it is also registered.

(b) No blood product may be imported from a foreign establishment into the United States except a blood product imported or offered for import pursuant to the investigational use provisions of part 312 of this chapter, unless it is first the subject of a blood product listing as required in Subpart B of this part. The blood product listing information shall be in the English language.

(c) Foreign establishments shall submit, as part of the blood product listing, the name and address of the establishment and the name of the individual responsible for submitting blood product listing information. Any changes in this information shall be reported to the Food and Drug Administration at the intervals specified for updating blood product listing information in § 607.30(a).

[40 FR 52788, Nov. 12, 1975, as amended at 55 FR 11014, Mar. 26, 1990]

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), (2), and (3) of the act, or because the Commissioner has found, under section 510(g)(4), that such registration is not necessary for the protection of the public health.

(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.

(g) Clinical laboratories that are approved for Medicare reimbursement and are engaged in the testing of blood products in support of other registered blood establishments.

[40 FR 52788, Nov. 12, 1975, as amended at 43 FR 37997, Aug. 25, 1978; 45 FR 85729, Dec. 30, 1980; 49 FR 34449, Aug. 31, 1984]

PART 610—GENERAL BIOLOGICAL PRODUCTS STANDARDS

Subpart A—Release Requirements

Subpart B—General Provisions

Subpart C—Standard Preparations and Limits of Potency

Subpart D—Mycoplasma

Subpart E—Hepatitis Requirements

Subpart F—Dating Period Limitations

Subpart G—Labeling Standards

AUTHORITY: Secs. 201, 501, 502, 503, 505, 510, 701 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, 351, 352, 353, 355, 360, 371); secs. 215, 351, 352, 353, 361 of the Public Health Service Act (42 U.S.C. 216, 262, 263, 263a, 264).

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

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

Subpart A—Release Requirements

§ 610.1 Tests prior to release required for each lot.

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

§ 610.2 Requests for samples and protocols; official release.

(a) *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.

(Information collection requirements approved by the Office of Management and Budget under control number 0910–0206)

[40 FR 31313, July 25, 1975, as amended by 49 FR 23834, June 8, 1984; 50 FR 10941, Mar. 19, 1985; 55 FR 11013 and 11014, Mar. 26, 1990]

Subpart B—General Provisions

§ 610.9 Equivalent methods and processes.

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

(a) The manufacturer presents evidence, in the form of a product license supplement, 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 (HFB–1), 8800 Rockville Pike, Bethesda, MD 20892.

[49 FR 15187, Apr. 18, 1984; 49 FR 21317, May 21, 1984, as amended at 51 FR 15607, Apr. 25, 1986; 55 FR 11014, Mar. 26, 1990; 59 FR 49351, Sept. 28, 1994]

§ 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.* The test prescribed in this section need not be performed for Whole Blood, Red Blood Cells, Cryoprecipitated AHF, Platelets, or Plasma.

[41 FR 10891, Mar. 15, 1976, as amended at 49 FR 15187, Apr. 18, 1984; 49 FR 23834, June 8, 1984; 50 FR 4133, Jan. 29, 1985; 51 FR 15607, Apr. 25, 1986; 55 FR 11013, Mar. 26, 1990; 59 FR 49351, Sept. 28, 1994]

§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

1-cystine	0.5 Gm.
Sodium chloride	2.5 Gm.
Dextrose ($C_6H_{12}O_6 \cdot H_2O$)	5.5 Gm.
Granular agar (less than 15% moisture by weight).	0.75 Gm.
Yeast extract (water-soluble)	5.0 Gm.
Pancreatic digest of casein	15.0 Gm.
Purified water	1,000.0 ml.
Sodium thioglycollate (or thioglycolic acid—0.3 ml).	0.5 Gm.
Resazurin (0.10% solution, 1.0 ml. freshly prepared).	
pH after sterilization 7.1±0.2.	

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

SOYBEAN-CASEIN DIGEST MEDIUM

Pancreatic Digest of Casein	17.0 Gm.
Papaic Digest of Soybean Meal	3.0 Gm.
Sodium Chloride	5.0 Gm.
Dibasic Potassium Phosphate	2.5 Gm.
Dextrose ($C_6H_{12}O_6 \cdot H_2O$)	2.5 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 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.

Medium	Test microorganisms	Incubation temperature
	Spore-formers	
Fluid Thioglycollate	1. *Bacillus subtilis* (ATCC No. 6633)	30 to 35 °C.
	2. *Clostridium sporogenes* (ATCC No. 11437)	Do.
	Non-spore-formers	
	3. *Candida albicans* (ATCC No. 10231)	Do.
	4. *Micrococcus luteus* (ATCC No. 9341)	Do.
	5. *Bacteroides vulgatus* (ATCC No. 8482)	Do.
	Spore-formers	
Soybean-Casein Digest	1. *Bacillus subtilis* (ATCC No. 6633)	20 to 25 °C.
	Non-spore-formers	
	2. *Candida albicans* (ATCC No. 10231)	Do.
	3. *Micrococcus luteus* (ATCC No. 9341)	Do.

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 temperatre 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 (21st Revision, 1985), section entitled ''Test Procedures Using Membrane Filtration,'' p. 1159, which is incorporated by reference (copies are available from the United States Pharmacopeial Convention Inc., 12601 Twinbrook Parkway, Rockville, MD 20852, or available for inspection at the Office of the Federal Register, 800 North Capitol Street, NW., suite 700, Washington, DC 20408), 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, Smallpox Vaccine, Reagent Red Blood Cells, Anti-Human Globulin, or Blood Grouping Reagent.

(ii) Where a manufacturer submits data which the Director, Center for Biologics Evaluation and Research, finds adequate to establish that the mode of administration, the method of preparation, or the special nature of the product precludes or does not require a sterility test or that the sterility of the lot is not necessary to assure the safety, purity, and potency of the product, the Director may exempt a product from the sterility requirements of this section subject to any conditions necessary to assure the safety, purity, and potency of the product.

(5) *Number of final containers more than 20, less than 200.* If the number of final containers in the filling is more than 20 or less than 200, the sample shall be no less than 10 percent of the containers.

(6) *Number of final containers—20 or less.* If the number of final containers in a filling is 20 or less, the sample shall be two final containers, or the sample need be no more than one final container, provided (i) the bulk material met the sterility test requirements and (ii) after filling, it is demonstrated by testing a simulated sample that all surfaces to which the product was exposed were free of contaminating microorganisms. The simulated sample shall be prepared by rinsing the filling equipment with sterile 1.0 percent peptone solution, pH 7.1±0.1, which shall be discharged into a final container by the same method used for filling the final containers with the product.

(7) *Samples—large volume of product in final containers.* For Albumin (Human) and Plasma Protein Fraction (Human), when the volume of product in the final container is 50 milliliters or more, the final containers selected as the test sample may contain less than the full volume of product in the final containers of the filling from which the sample is taken: *Provided,* That the containers and closures of the sample are identical with those used for the filling to which the test applies, and the sample represents all stages of that filling.

(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.

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

(Information collection requirements approved by the Office of Management and Budget under control number 0910–0139)

[38 FR 32056, Nov. 20, 1973, as amended at 41 FR 4015, Jan. 28, 1976; 41 FR 10428, Mar. 11, 1976; 44 FR 11754, Mar. 2, 1979; 49 FR 15187, Apr. 18, 1984; 49 FR 23834, June 8, 1984; 50 FR 4133, Jan. 29, 1985; 51 FR 44906, Dec. 15, 1986; 53 FR 12764, Apr. 19, 1988; 55 FR 11013, Mar. 26, 1990]

§ 610.13 Purity.

Products shall be free of extraneous material except that which is unavoidable in the manufacturing process described in the approved license. 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 product 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.

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

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

(1) *Test dose.* The test dose for each rabbit shall be at least 3 milliliters per kilogram of body weight of the rabbit and also shall be at least equivalent proportionately, on a body weight basis, to the maximum single human dose recommended, but need not exceed 10 milliliters per kilogram of body weight of the rabbit, except that: (i) Regardless of the human dose recommended, the test dose per kilogram of body weight of each rabbit shall be at least 1 milliliter for immune globulins derived from human blood; (ii) for Streptokinase, the test dose shall be at least equivalent proportionately, on a body weight basis, to the maximum single human dose recommended.

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

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

(Information collection requirements were approved by the Office of Management and Budget (OMB) and assigned OMB control number 0910–0139)

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

§ 610.14 Identity.

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

§ 610.15 Constituent materials.

(a) *Ingredients, preservatives, diluents, adjuvants.* All ingredients used in a licensed product, and any diluent provided as an aid in the administration of the product, shall meet generally accepted standards of purity and quality. Any preservative used shall be sufficiently nontoxic so that the amount present in the recommended dose of the product will not be toxic to the recipient, and in the combination used it shall not denature the specific substances in the product to result in a decrease below the minimum acceptable potency within the dating period when stored at the recommended temperature. Products in multiple-dose containers shall contain a preservative, except that a preservative need not be added to Yellow Fever Vaccine; Poliovirus Vaccine Live Oral; viral vaccines

labeled for use with the jet injector; dried vaccines when the accompanying diluent contains a preservative; or to an Allergenic Product in 50 percent or more volume in volume (v/v) glycerin. An adjuvant shall not be introduced into a product unless there is satisfactory evidence that it does not affect adversely the safety or potency of the product. The amount of aluminum in the recommended individual dose of a biological product shall not exceed:

(1) 0.85 milligrams if determined by assay;

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

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

(b) *Extraneous protein; cell culture produced vaccines.* Extraneous protein known to be capable of producing allergenic effects in human subjects shall not be added to a final virus medium of cell culture produced vaccines intended for injection. If serum is used at any stage, its calculated concentration in the final medium shall not exceed 1:1,000,000.

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

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

§ 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.

(Approved by the Office of Management and Budget under control number 0910–0139)

[38 FR 32056, Nov. 20, 1973, as amended at 51 FR 44453, Dec. 10, 1986; 55 FR 11013, Mar. 26, 1990]

§ 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]

Subpart C—Standard Preparations and Limits of Potency

§ 610.20 Standard preparations.

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

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

ANTIBODIES

Botulism Antitoxin, Type A.
Botulism Antitoxin, Type B.
Botulism Antitoxin, Type E.
Diphtheria Antitoxin.
Histolyticus Antitoxin.
Oedematiens Antitoxin.
Perfringens Antitoxin.
Antipertussis Serum.
Antirabies Serum.
Sordellii Antitoxin.
Staphylococcus Antitoxin.
Tetanus Antitoxin.
Vibrion Septique Antitoxin.

ANTIGENS

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

BLOOD DERIVATIVE

Thrombin.

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

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

§ 610.21 Limits of potency.

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

ANTIBODIES

Diphtheria Antitoxin, 500 units per milliliter.
Tetanus Antitoxin, 400 units per milliliter.
Tetanus Immune Globulin (Human), 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 CO_2 in N_2. Aerobic incubation shall be for a period of no less than 14 days and the broth in the two tubes shall be tested after 3 days and 14 days, at which times 0.5 ml. of broth from each of the two tubes shall be combined and subinoculated on to no less than 4 additional plates and incubated aerobically. Anaerobic incubation shall be for no less than 14 days and the broth in the two tubes shall be tested after 3 days and 14 days, at which times 0.5 ml. of broth from each of the two tubes shall be combined and subinoculated onto no less than four additional plates and incubated anaerobically. All inoculated plates shall be incubated for no less than 14 days, at which time observation for growth of *Mycoplasma* shall be made at a magnification of no less than 300×. If the Dienes Methylene Blue-Azure dye or an equivalent staining procedure is used, no less than a one square cm. plug of the agar shall be excised from the inoculated area and examined for the presence of *Mycoplasma.* The presence of the *Mycoplasma* shall be determined by comparison of the growth obtained from the test samples with that of the control cultures, with respect to typical colonial and microscopic morphology. The virus pool is satisfactory for vaccine manufacture if none of the tests on the samples show evidence of the presence of *Mycoplasma.*

Subpart E—Hepatitis Requirements

§ 610.40 Test for hepatitis B surface antigen.

(a) *Test sensitivity.* Each donation of blood, plasma, or serum to be used in preparing a biological product shall be tested for the presence of hepatitis B surface antigen by a method of sufficient sensitivity to detect all sera labeled A, (A), B, (B), and C in the Reference Hepatitis B Surface Antigen Panel distributed by the Center for Biologics Evaluation and Research; except that, in emergency situations, a test method of sufficient sensitivity to detect all sera labeled A, (A), and B in the Reference Hepatitis B Surface Antigen Panel may be used and, in dire emergency situations, blood and blood products may be issued without any HB_8 Ag testing, provided that a test otherwise required by this paragraph is performed as soon as possible after issuance of the blood and blood product.

(b) *Procedures.* Only Antibody to Hepatitis B Surface Antigen licensed under this subchapter shall be used in performing the test and the test method(s) used shall be that for which the antibody product is specifically designed to be effective as recommended by the manufacturer in the package insert. The sample of blood, plasma, or serum to be tested shall have been taken from the donor at the time of donation of that unit. The test need not be performed on the day of the withdrawal of the sample. If the radioimmunoassay method is used, it must be performed in one of the following ways:

(1) The complete test is performed at the collection facility.

(2) The test is performed at the collection facility up to the point of counting the radioactivity of the samples, which counting, thereafter, is performed at another facility by personnel from the collection facility or by personnel from the counting facility.

(3) The complete test is performed by the personnel at an establishment licensed to manufacture blood or blood derivatives under section 351(a) of the

Public Health Service Act (42 U.S.C. 262(a)), or by a clinical laboratory which meets the standards of the Clinical Laboratories Improvement Act of 1967 (CLIA) (42 U.S.C. 263a), provided the establishment or the clinical laboratory is qualified to perform radioimmunoassay testing for the presence of hepatitis B surface antigen.

(4) Except as provided in this paragraph (b)(4), a collection facility shall not ship any blood product as a biological product or ship such a blood product where it is intended for use in manufacturing a biological product until the test for hepatitis B surface antigen is completed and the written test results are received by the collection facility. Notwithstanding the provisions of §610.1 of this chapter, in the case of an emergency, or as otherwise approved in writing by the Director, Center for Biologics Evaluation and Research, a collection facility may ship a blood product before the test for hepatitis B surface antigen is completed. To obtain approval for such shipments, the collection facility shall submit a description of the control procedures to be used by both the collection facility and the manufacturing facility to the Director, Center for Biologics Evaluation and Research (HFB–1), Food and Drug Administration, 8800 Rockville Pike, Bethesda, MD 20892. The control procedures to be used by the collection facility and the manufacturing facility shall include, but may not be limited to, a system of communicating the test results to the manufacturing facility, use of specific labeling warnings for the product to ensure that persons handling the shipment know that it may be infectious, procedures for quarantine of the untested or incompletely tested product both at the collection facility and at the manufacturing facility, and a procedure at the manufacturing facility to identify, preclude use of, and dispose of any blood product that is received and later found to be reactive for hepatitis B surface antigen.

(c) *Materials in storage.* All blood, plasma, or serum in storage which has not been tested for the presence of the hepatitis B surface antigen shall be tested as required in paragraphs (a) and (b) of this section before use as a biological product, or before use in the manufacture of a biological product. All blood, plasma, or serum in storage which has been tested for the presence of the hepatitis B surface antigen by a method of second generation sensitivity may be used as a biological product or in manufacture of a biological product, provided it is used on or before March 15, 1976.

(d) *Restrictions on use.* Blood, plasma, or serum that is reactive when tested for hepatitis B surface antigen or that was collected from a donor known to be reactive for hepatitis B surface antigen shall not be used in manufacturing biological products except as provided in paragraphs (d) (1) and (2) of this section.

(1) *Injectable biological products and licensed in vitro diagnostic biological products.* Blood, plasma, or serum that is reactive when tested for hepatitis B surface antigen or that was collected from a donor known to be reactive for hepatitis B surface antigen may be used in manufacturing hepatitis B vaccine and licensed in vitro diagnostic biological products if all of the following conditions are met:

(i) The final product cannot be prepared from blood, plasma, or serum that is nonreactive when tested for hepatitis B surface antigen, due either to the nature or to the scarcity of the final product.

(ii) The label of the source blood, plasma, or serum conspicuously states either that it is reactive when tested for hepatitis B surface antigen and it may transmit viral hepatitis; or that the source blood, plasma, or serum was collected from a donor known to be reactive for hepatitis B surface antigen and it may transmit viral hepatitis, although confirmatory hepatitis testing has not been done.

(iii) The package label of the licensed in vitro diagnostic biological product prepared from such blood, plasma, or serum states conspicuously that either the product was prepared from source material that was reactive when tested for hepatitis B surface antigen and it may transmit viral hepatitis; or that the source material was collected from a donor known to be reactive for hepatitis B surface antigen and it may

transmit viral hepatitis, although confirmatory hepatitis testing has not been done.

(iv) The package label of the licensed injectable biological product prepared from such blood, plasma, or serum states that the product has been inactivated.

(v) The Director, Center for Biologics Evaluation and Research (HFB–1), Food and Drug Administration, 8800 Rockville Pike, Bethesda MD 20892, is notified in writing at the time of the shipment, or in the case of repetitive shipments, or April 1 and October 1 of each year, of each shipment of source blood, plasma, or serum for manufacture into hepatitis B vaccine or into a licensed in vitro diagnostic biological product. Such shipments shall not be subject to the requirements of paragraph (b)(3) of this section. Each notification shall identify the kind and amount of source material shipped, the name and address of the consignee, the date of shipment, and the manner in which the source material is labeled.

(2) *Unlicensed in vitro diagnostic biological products.* Blood, plasma, or serum that is reactive when tested for hepatitis B surface antigen or that was collected from a donor known to be reactive for hepatitis B surface antigen may be used in manufacturing unlicensed in vitro diagnostic biological products including clinical chemistry control reagents if all of the following conditions are met:

(i) The final product cannot be prepared from blood, plasma, or serum that is nonreactive when tested for hepatitis B surface antigen, due either to the nature or to the scarcity of the final product.

(ii) The label of the source blood, plasma, or serum states conspicuously that either it is reactive when tested for hepatitis B surface antigen and it may transmit viral hepatitis; or that the source blood, plasma, or serum was collected from a donor known to be reactive for hepatitis B surface antigen and it may transmit viral hepatitis, although confirmatory hepatitis testing has not been done.

(iii) The manufacturer of the source blood, plasma, or serum obtains written assurance from the manufacturer(s) of the final unlicensed product that package labels of all unlicensed products will conspicuously state, as required by §809.10(a)(4) of this chapter, that the product was prepared from blood, plasma, or serum that was reactive when tested for hepatitis B surface antigen and it may transmit viral hepatitis; or that the source material was collected from a donor known to be reactive for hepatitis B surface antigen and it may transmit viral hepatitis, although confirmatory hepatitis testing has not been done.

(iv) At the time of shipment, the Director, Center for Biologics Evaluation and Research (HFB–1), Food and Drug Administration, 8800 Rockville Pike, Bethesda, MD 20892, is notified in writing of each shipment of source blood, plasma, or serum signifying the kind and the amount of source material shipped, the name and address of the consignee, the date of shipment, and the manner in which such source material was labeled. Such shipments shall not be subject to the requirements of paragraph (b)(3) of this section.

(e) *Manufacturing responsibility.* When the radioimmunoassay method for hepatitis B surface antigen testing is performed by personnel other than those of the facility collecting the blood, plasma, or serum, as provided in paragraph (b) of this section, it shall not be considered as divided manufacturing as described in §610.63, provided the following conditions are met:

(1) The collecting facility 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.

(2) The testing laboratory will participate in any proficiency testing programs undertaken by the Center for Biologics Evaluation and Research, Food and Drug Administration.

(f) The information collection requirements in paragraph (d) of this section were approved by the Office of

Management and Budget and assigned OMB control number 0910–0136.

(Information collection requirements contained in paragraph (b)(4) were approved by the Office of Management and Budget under control number 0910–0168)

[40 FR 29710, July 15, 1975, as amended at 48 FR 23181, May 24, 1983; 49 FR 23834, June 8, 1984; 49 FR 26718, June 29, 1984; 51 FR 15607, Apr. 25, 1986; 55 FR 11013 and 11014, Mar. 26, 1990]

§ 610.41 History of hepatitis B surface antigen.

A person known to have previously tested positive for hepatitis B surface antigen, testing positive, or both, may not serve as a donor of human blood, plasma, or serum, except that under § 640.120 of this chapter, such a donor may serve as a source of hepatitis B surface antigen for the manufacture of hepatitis B vaccine or the preparation of a diagnostic product for laboratory tests, or a person known to have previously tested positive for hepatitis B surface antigen may serve as a source of antibody to hepatitis B surface antigen for the preparation of a biological product or a diagnostic product for laboratory tests.

[48 FR 23182, May 24, 1983, as amended at 57 FR 10814, Mar. 31, 1992]

§ 610.45 Human Immunodeficiency Virus (HIV) requirements.

(a) *Testing requirements.* (1) Each donation of human blood or blood components intended for use in preparing a product shall be tested for antibody to HIV by a test approved for such use by FDA, except as otherwise approved in writing by FDA. When the test for antibody to HIV is required, blood and blood products may be issued before the results of the test for antibody to HIV are available only in dire emergency situations or as otherwise approved in writing by FDA and, provided the test required by this paragraph is performed as soon as possible after issuance of the blood or blood product.

(2) Tests approved by FDA for the screening of blood and blood components for evidence of HIV may only be used in place of a test for antibody to HIV to satisfy the requirements of this section and related sections if so specified by FDA.

(b) *Testing responsibility.* The test for antibody to HIV shall be performed by the collection facility, by personnel of an establishment licensed to manufacture blood or blood derivatives under section 351(a) of the Public Health Service Act (42 U.S.C. 262(a)), or by a clinical laboratory which meets the standards of the Clinical Laboratory Improvement Act of 1967 (CLIA) (42 U.S.C. 263a), provided the establishment or clinical laboratory is qualified to perform the test.

(c) *Restrictions on use.* (1) Blood, plasma, or other blood components that are repeatably reactive to a test for antibody to HIV or that were collected from a donor whose blood is known to be repeatably reactive to a test for antibody to HIV, shall not be shipped or used to prepare any product, including products not subject to licensure; except that such blood and blood components shall be shipped or used only for purposes and under conditions specifically approved in writing by FDA.

(2) The restrictions on use contained in this paragraph shall not apply in the following cases:

(i) Blood and blood components testing repeatably reactive or from a donor whose blood is known to be repeatably reactive that are shown to be negative for evidence of HIV infection by a method or process approved for such use by FDA;

(ii) The distribution of blood, plasma, or serum samples, except when intended for use in the manufacture of a product;

(iii) The in-house use of blood and blood components for research purposes; or

(iv) The distribution of blood and blood components for research purposes, if not distributed by sale, barter, or exchange.

[53 FR 116, Jan. 5, 1988]

Subpart F—Dating Period Limitations

§ 610.50 Date of manufacture.

The date of manufacture shall be determined as follows:

(a) For products for which an official standard of potency is prescribed in either § 610.20 or § 610.21, or which are subject to official potency tests, the date of initiation by the manufacturer of the last valid potency test.

(b) For products that are not subject to official potency tests, (1) the date of removal from animals, (2) the date of extraction, (3) the date of solution, (4) the date of cessation of growth, or (5) the date of final sterile filtration of a bulk solution, whichever is applicable.

[38 FR 32056, Nov. 20, 1973, as amended at 42 FR 27582, May 31, 1977]

§ 610.53 Dating periods for licensed biological products.

(a) *General.* The minimum dating periods in paragraph (c) of this section are based on data relating to usage, clinical experience, or laboratory tests that establish the reasonable period beyond which the product cannot be expected to yield its specific results and retain its safety, purity, and potency, provided the product is maintained at the recommended temperatures. The standards prescribed by the regulations in this subchapter are designed to ensure the continued safety, purity, and potency of the products and are based on the dating periods set forth in paragraph (c) of this section. Package labels for each product shall recommend storage at the stated temperatures.

(b) *When the dating period begins.* The dating period for a product shall begin on the date of manufacture, as prescribed in § 610.50. The dating period for a combination of two or more products shall be no longer than the dating period of the component with the shortest dating period.

(c) *Table of dating periods.* In using the table in this paragraph, a product in column A may be stored by the manufacturer at the prescribed temperature and length of time in either column B or C, plus the length of time in column D. The dating period in column D shall be applied from the day the product leaves the manufacturer's storage, provided the product has not exceeded its maximum storage period, as prescribed in column B or C. If a product is held in the manufacturer's storage beyond the period prescribed, the dating period for the product being distributed shall be reduced by a corresponding period.

Product	Manufacturer's storage period 1 to 5 °C (unless otherwise stated)	Manufacturer's storage period 0 °C or colder (unless otherwise stated)	Dating period after leaving manufacturer's storage when stored at 2 to 8 °C (unless otherwise stated)
A	B	C	D
Adenovirus Vaccine Live Oral	6 months	Not applicable	6 months.
Albumin (Human)	3 years	.....do	(a) 5 years.
	.....do	.....do	(b) 3 years, provided labeling recommends storage at room temperature, no warmer than 37 °C.
	Not applicable	.....do	(c) 10 years, if in a hermetically sealed metal container and provided labeling recommends storage between 2 and 8 °C.
Allergenic Extracts labeled "No U.S. Standard of Potency":			
1. With 50 percent or more glycerin	3 years	.....do	3 years.
2. With less than 50 percent glycerin	18 months	.....do	18 months.
3. Products for which cold storage conditions are inappropriate.	Not applicable	.....do	18 months (from date of manufacture), provided labeling recommends storage at 30 °C or colder.
4. Powders and tablets	.....do	.....do	5 years (from date of manufacture), provided labeling recommends storage at 30 °C or colder.
5. Freeze-dried products:			
a. Unreconstituted	.....do	.....do	4 years (from date of manufacture).
b. Reconstituted	.....do	.....do	18 months (cannot exceed 4-year unreconstituted dating period plus an additional 12 months).
Allergenic Extracts, Alum Precipitated labeled "No U.S. Standard of Potency'.	18 months	.....do	18 months.
Anthrax Vaccine Adsorbed	2 years	.....do	1 year.

Product	Manufacturer's storage period 1 to 5 °C (unless otherwise stated)	Manufacturer's storage period 0 °C or colder (unless otherwise stated)	Dating period after leaving manufacturer's storage when stored at 2 to 8 °C (unless otherwise stated)
A	B	C	D
Antibody to Hepatitis B Surface Antigen:			
1. Antibody to Hepatitis B Surface Antigen.	6 months	.....do	6 months.
2. Lyophilized coated red blood cells	.....do	.....do	Do.
3. Enzyme conjugated products	.....do	.....do	Do.
Iodinated (^{125}I) products	Not applicable	.....do	45 days (from date of manufacture).
Antihemophilic Factor (Human)	.....do	.....do	1 year (from date of manufacture).
Anti-Human Globulin Liquid	.....do	.....do	2 years.
Anti-Inhibitor Coagulant Complex	.....do	.....do	Do.
Antirabies Serum	1 year	.....do	Do.
Antivenin (*Crotalidae*) Polyvalent	.....do	.....do	5 years with an initial 10 percent excess of potency, provided labeling recommends storage at 37 ° C or colder.
Antivenin (*Latrodectus Mactans*)	.....do	.....do	5 years with an initial 10 percent excess of potency.
Antivenin (*Micurus fulvius*)	.....do	.....do	Do.
Asparaginase	Not applicable	.....do	18 months from the date of the last valid potency test.
BCG Vaccine	1 year	Not applicable	6 months.
Blood Grouping Reagents			
1. Liquid	Not applicable	Not applicable	2 years.
2. Dried	1 year	2 years	5 years.
Blood Group Substance AB	.....do	.....do	2 years.
Blood Group Substance A	.....do	.....do	Do.
Blood Group Substance B	.....do	.....do	Do.
Botulism Antitoxin	.....do	Not applicable	5 years with an initial 20 percent excess of potency.
Cholera Vaccine	.....do	.....do	18 months.
Coccidioidin	.....do	.....do	3 years.
Collagenase	Not applicable	.....do	4 years (from date of manufacture), provided labeling recommends storage at 37 °C or colder.
Cryoprecipitated AFH	.....do	.....do	12 months from the date of collection of source blood, provided labeling recommends storage at −18 °C or colder.
Diphtheria Antitoxin:			
1. Liquid	1 year	.....do	5 years with an initial 20 percent excess of potency.
2. Dried	.....do	2 years	5 years with an initial 10 percent excess of potency.
Diphtheria and Tetanus Toxoids and Pertussis Vaccine Adsorbed.	.....do	Not applicable	18 months.
Diphtheria and Tetanus Toxoids, Adsorbed	.....do	.....do	2 years.
Diphtheria Toxin for Schick Test	.....do	.....do	1 year.
Diphtheria Toxoid	.....do	.....do	2 years.
Diphtheria Toxoid Adsorbed	.....do	2 years	Do.
Diphtheria Toxoid-Schick Test Control	Not applicable	Not applicable	1 year.
Factor IX Complex	.....do	.....do	1 year (from date of manufacture).
Fibrinolysin (Human)	1 year	2 years	2 years.
Fibrinolysin and Desoxyribonuclease Combined (Bovine).	.....do	.....do	3 years, provided labeling recommends storage at 30 °C or colder.
Fibrinolysin and Desoxyribonuclease Combined (Bovine) with Chloramphenicol.	.....do	.....do	Do.
Hepatitis B Surface Antigen:			
1. Unlyophilized coated red blood cells.	Not applicable	.....do	14 days (from date of manufacture).
2. Iodinated (^{125}I) product	.....do	.....do	45 days (from date of manufacture).
3. Enzyme conjugated product	6 months	.....do	6 months.
Histoplasmin	1 year	Not applicable	2 years.
Immunoglobulins:			
1. Hepatitis B Immune Globulin (Human).	Not applicable	.....do	1 year.
2. Immune Globulin (Human)	3 years	.....do	3 years.
3. Immune Globulin Intravenous (Human).	Not applicable	.....do	1 year.
4. Lymphocyte Immune Globulin, Anti-Thymocyte Globulin (Equine).	.....do	Not applicable	2 years.
5. Pertussis Immune Globulin (Human).	3 years	.....do	3 years from date the dried or frozen bulk product is placed in final solution.

Product	Manufacturer's storage period 1 to 5 °C (unless otherwise stated)	Manufacturer's storage period 0 °C or colder (unless otherwise stated)	Dating period after leaving manufacturer's storage when stored at 2 to 8 °C (unless otherwise stated)
A	B	C	D
6. Rabies Immune Globulin (Human)	1 year	.....do	1 year.
7. Rh_o(D) Immune Globulin (Human)	6 months	.....do	6 months.
8. Tetanus Immune Globulin (Human)	1 year	.....do	3 years with an initial 10 percent excess of potency.
9. Vaccinia Immune Globulin (Human)	3 years	.....do	3 years.
10. Varicella-Zoster Immune Globulin (Human).	Not applicable	.....do	1 year.
Hepatitis B Vaccine	2 years at 2 to 8 °C.	Not applicable	3 years.
Influenza Virus Vaccine	1 year	.....do	18 months.
Limulus Amebocyte Lysate	Not applicable	Not applicable	18 months (from date of manufacture).
Measles, Mumps, and Rubella Virus Vaccine Live.	.....do	1 year (−20 °C or colder).	1 year.
Measles and Mumps Virus Vaccine Live	.....do	.....do	1 year.
Measles and Rubella Virus Vaccine Live	.....do	.....do	Do.
Measles Live and Smallpox Vaccine	Not applicable	.....do	1 year (from date of manufacture).
Measles Virus Vaccine Live	.....do	.....do	1 year.
Meningococcal Polysaccharide Vaccine Group A:			
1. Final bulk powder	.....do	2 years (−20 °C or colder).	Not applicable.
2. Final container	Not applicable	3 years (−20 °C or colder).	2 years.
Meningococcal Polysaccharide Vaccine Group C:			
1. Final bulk powder	.....do	2 years (−20 °C or colder).	Not applicable.
2. Final container	.....do	3 years (−20 °C or colder).	2 years.
Meningococcal Polysaccharide Vaccine Groups A and C combined:			
1. Final bulk powder	.....do	2 years (−20 °C or colder).	Not applicable.
2. Final container	.....do	3 years (−20 °C or colder).	2 years.
Meningococcal Polysaccharide Vaccine Groups A, C, Y, and W135 combined:			
1. Final bulk power	.....do	2 years (−20 °C or colder).	Not applicable.
2. Final container	.....do	3 years (−20 °C or colder).	2 years.
Mumps Skin Test Antigen	6 months	Not applicable	18 months.
Mumps Virus Vaccine Live	Not applicable	1 year (−20 °C or colder).	1 year.
Normal Horse Serum	1 year	2 years	5 years.
Pertussis Vaccine	.....do	Not applicable	18 months.
Pertussis Vaccine Adsorbed	.....do	.....do	Do.
Plague Vaccine	.....do	.....do	Do.
Plasma products:			
1. Fresh Frozen Plasma	Not applicable	.....do	1 year from date of collection of source blood (−18 °C or colder).
2. Liquid Plasma	.....do	.....do	(a) 26 days from date of collection of source blood (between 1 and 6 °C). (b) 40 days from date of collection of source blood only when CPDA–1 solution is used as the anticoagulant (between 1 and 6 °C).
3. Plasma	.....do	.....do	5 years from date of collection of source blood (−18 °C or colder).
4. Platelet Rich Plasma	.....do	.....do	72 hours from time of collection of source blood, provided labeling recommends storage (20 to 24 °C or between 1 and 6 °C). 5 days if certain approved containers are used (20 to 24 °C).
5. Source Leukocytes	.....do	.....do	In lieu of expiration date, the collection date shall appear on the label.
6. Source Plasma	.....do	.....do	10 years (at the recommended storage temperature stated on the label).

Product	Manufacturer's storage period 1 to 5 °C (unless otherwise stated)	Manufacturer's storage period 0 °C or colder (unless otherwise stated)	Dating period after leaving manufacturer's storage when stored at 2 to 8 °C (unless otherwise stated)
A	B	C	D
7. Therapeutic Exchange Plasma	.....do	.....do	10 years.
Plasma Protein Fraction (Human)	1 year	.....do	(a) 5 years. (b) 3 years provided labeling recommends storage at room temperature, no warmer than 30 °C).
Platelets	Not applicable	.....do	72 hours from time of collection of source blood, provided labeling recommends storage at 20 to 24 °C or between 1 and 6 °C. 5 days if certain approved containers are used (20 to 24 °C).
Pneumococcal Vaccine Polyvalent:			
1. Final bulk powder	.....do	24 months after potency assay (−20 °C or colder).	Not applicable.
2. Final container	.....do	Not applicable	2 years (from date of manufacture).
Poliovirus Vaccine Inactivated	1 year	.....do	1 year.
Poliovirus Vaccine Live Oral Trivalent:			
1. Frozen	Not applicable	1 year (−10 °C or colder).	1 year, provided labeling recommends storage at a temperature which will maintain ice continuously in a solid state.
2. Liquid	.....do	Not applicable	30 days, provided labeling recommends storage between 2 and 8 °C and container has been unopened.
Poliovirus Vaccine Live Oral Type I:			
1. Frozen	.....do	1 year (−10 °C or colder).	1 year, provided labeling recommends storage at a temperature which will maintain ice continuously in a solid state.
2. Liquid	.....do	Not applicable	30 days, provided labeling recommends storage between 2 and 8 °C and container has been unopened.
Poliovirus Vaccine Live Oral Type II:			
1. Frozen	.....do	1 year (−10 °C or colder).	1 year, provided labeling recommends storage at a temperature which will maintain ice continuously in a solid state.
2. Liquid	.....do	Not applicable	30 days, provided labeling recommends storage between 2 and 8 °C and container has been unopened.
Poliovirus Vaccine Live Oral Type III:			
1. Frozen	.....do	1 year (−10 °C or colder).	1 year, provided labeling recommends storage at a temperature which will maintain ice continuously in a solid state.
2. Liquid	.....do	Not applicable	30 days, provided labeling recommends storage between 2 and 8 °C and container has been unopened.
Polyvalent bacterial antigens with ''No U.S. Standard of Potency'' liquid.	1 year	.....do	18 months.
Polyvalent bacterial vaccines with ''No U.S. Standard of Potency'' liquid.	.....do	.....do	Do.
Rabies Vaccine:			
1. Dried	.....do	2 years	Do.
2. Liquid	3 months	Not applicable	6 months.
Reagent red blood cells	Not applicable	Not applicable	Thirty-five days from earliest date of collection if kept in liquid form (indefinite storage of reagent red blood cell source material at −65 °C or colder).

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

Product	Manufacturer's storage period 1 to 5 °C (unless otherwise stated)	Manufacturer's storage period 0 °C or colder (unless otherwise stated)	Dating period after leaving manufacturer's storage when stored at 2 to 8 °C (unless otherwise stated)
A	B	C	D
ACD Whole Blood	Not applicable	do	21 days from date of collection, provided labeling recommends storage between 1 and 6 °C.
CPD Whole Blood	do	do	Do.
CPDA–1 Whole Blood	do	do	35 days from date of collection, provided labeling recommends storage between 1 and 6 °C.
Heparin Whole Blood	do	do	48 hours from date of collection, provided labeling recommends storage between 1 and 6 °C.
Yellow Fever Vaccine	do	1 year (−20 °C or colder).	1 year, provided labeling recommends storage at 5 °C or colder.

(d) *Exemptions.* Exemptions or modifications shall be made only upon written approval, in the form of a supplement of the product license, issued by the Director, Center for Biologics Evaluation and Research (HFB–1).

[50 FR 4134, Jan. 29, 1985, as amended at 51 FR 15607, Apr. 25, 1986; 51 FR 19750, June 2, 1986; 52 FR 37450, Oct. 7, 1987; 53 FR 12764, Apr. 19, 1988; 55 FR 11014, Mar. 26, 1990; 59 FR 49351, Sept. 28, 1994]

Subpart G—Labeling Standards

§ 610.60 Container label.

(a) *Full label.* The following items shall appear on the label affixed to each container of a product capable of bearing a full label:

(1) The proper name of the product;

(2) The name, address, and license number of manufacturer;

(3) The lot number or other lot identification;

(4) The expiration date;

(5) The recommended individual dose, for multiple dose containers.

(6) The statement: ''Caution: Federal law prohibits dispensing without prescription,'' for prescription biologicals.

(b) *Package label information.* If the container is not enclosed in a package, all the items required for a package label shall appear on the container label.

(c) *Partial label.* If the container is capable of bearing only a partial label, the container shall show as a minimum the name (expressed either as the proper or common name), the lot number or other lot identification and the name of the manufacturer; in addition, for multiple dose containers, the recommended individual dose. Containers bearing partial labels shall be placed in a package which bears all the items required for a package label.

(d) *No container label.* If the container is incapable of bearing any label, the items required for a container label may be omitted, provided the container is placed in a package which bears all the items required for a package label.

(e) *Visual inspection.* When the label has been affixed to the container a sufficient area of the container shall remain uncovered for its full length or circumference to permit inspection of the contents.

[38 FR 32056, Nov. 20, 1973, as amended at 47 FR 22518, May 25, 1982]

§ 610.61 Package label.

The following items shall appear on the label affixed to each package containing a product:

(a) The proper name of the product;

(b) The name, address, and license number of manufacturer;

(c) The lot number or other lot identification;

(d) The expiration date;

(e) The preservative used and its concentration, or if no preservative is used and the absence of a preservative is a safety factor, the words ''no preservative'';

(f) The number of containers, if more than one;

(g) The amount of product in the container expressed as (1) the number of doses, (2) volume, (3) units of potency,

(4) weight, (5) equivalent volume (for dried product to be reconstituted), or (6) such combination of the foregoing as needed for an accurate description of the contents, whichever is applicable;

(h) The recommended storage temperature;

(i) The words ''Shake Well'', ''Do not Freeze'' or the equivalent, as well as other instructions, when indicated by the character of the product;

(j) The recommended individual dose if the enclosed container(s) is a multiple-dose container;

(k) The route of administration recommended, or reference to such directions in an enclosed circular;

(l) Known sensitizing substances, or reference to an enclosed circular containing appropriate information;

(m) The type and calculated amount of antibiotics added during manufacture;

(n) The inactive ingredients when a safety factor, or reference to an enclosed circular containing appropriate information;

(o) The adjuvant, if present;

(p) The source of the product when a factor in safe administration;

(q) The identity of each microorganism used in manufacture, and, where applicable, the production medium and the method of inactivation, or reference to an enclosed circular containing appropriate information;

(r) Minimum potency of product expressed in terms of official standard of potency or, if potency is a factor and no U.S. standard of potency has been prescribed, the words ''No U.S. standard of potency.''

(s) The statement: ''Caution: Federal law prohibits dispensing without prescription,'' for prescription biologicals.

[38 FR 32056, Nov. 20, 1973, as amended at 47 FR 22518, May 25, 1982; 55 FR 10423, Mar. 21, 1990]

§ 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 establishments participate in the manufacture of a 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.

§ 610.64 Name of selling agent or distributor.

The name and address of the selling agent or distributor of a product may appear on the label under the designation of ''selling agent'' or ''distributor'' provided that the name and address of the manufacturer is given precedence in prominence.

§ 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 620—ADDITIONAL STANDARDS FOR BACTERIAL PRODUCTS

Subpart A—Pertussis Vaccine

Sec.

AUTHORITY: Secs. 201, 501, 502, 503, 505, 510, 701 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, 351, 352, 353, 355, 360, 371); secs. 215, 351, 352, 353, 361 of the Public Health Service Act (42 U.S.C. 216, 262, 263, 263a, 264).

SOURCE: 38 FR 32064, 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—Pertussis Vaccine

§ 620.1 Pertussis Vaccine.

The proper name of this product shall be ''Pertussis Vaccine'', which shall be an aqueous preparation of killed whole *Bordetella pertussis* bacteria. The vaccine may be precipitated or adsorbed and may be combined with other antigens.

[56 FR 63410, Dec. 4, 1991]

§ 620.2 Production.

(a) *Propagation of bacteria.* Human blood shall not be used in culture medium for propagating bacteria either for seed or for vaccine. The culture medium for propagating bacteria for vaccine shall not contain ingredients known to be capable of producing allergenic effects in human subjects, except blood or blood products from lower animals other than the horse. When blood or a blood product is used, it shall be removed by washing the harvested bacteria. The bacterial concentrate shall be free of extraneous bacteria, fungi, and yeasts, as demonstrated by microscopic examination and cultural methods.

(b) *Bacterial content.* (1) The opacity of the bacterial concentrate shall be determined in terms of the U.S. Opacity Standard not later than 2 weeks after the harvest of the bacteria and before any treatment capable of altering the opacity of the bacterial concentrate.

(2) The total immunizing dose of a vaccine prepared with whole bacteria shall contain (i) in the case of nonadsorbed vaccine no more bacteria than the equivalent of 60 opacity units and (ii) in the case of adsorbed vaccine no more than the equivalent of 48 opacity units.

(c) *Detoxification.* After removing a sample for purity testing, the bacteria shall be killed and detoxified either (1) by heating, (2) by addition of a chemical agent and appropriate aging, or (3) by any combination of the stated procedures. The procedure used shall be one that has been shown to have no adverse effect on required safety, purity, and potency.

(d) *Preservative.* The vaccine shall contain a preservative.

§ 620.3 U.S. Standard preparations.

(a) The U.S. Standard Pertussis Vaccine shall be used for determining the potency of Pertussis Vaccine.

(b) The U.S. Opacity Standard shall be used in estimating the bacterial content of the vaccine and of the challenge culture.

§ 620.4 Potency test.

The number of protective units of the total human immunizing dose shall be estimated for each lot of vaccine from the results of simultaneous intracerebral mouse protection tests of the vaccine under test and the U.S. Standard Pertussis Vaccine. The potency test shall be performed as follows:

(a) *Mice.* Healthy mice shall be used, all from a single strain and of the same sex, or an equal number of each sex in each group, with individual weight varying no more than 4 grams in a single test. In no event shall any of the mice weigh less than 10 grams or more than 20 grams. A system of randomization shall be used to distribute the mice into the groups, with respect to shelf position and to determine the order of challenge. There shall be at least 3 groups consisting of no less than 16 mice each, for each vaccine. In addition, there shall be at least 4 groups consisting of no less than 10 mice each, for control purposes: one group for the challenge dose and 3 groups for titrating the virulence of the challenge dose.

(b) *Vaccination.* (1) Five-fold serial dilutions of the vaccine to be tested and of the standard vaccine shall be made in 0.85 percent sodium chloride solution. The dilutions of the vaccine under test shall have the same protective unitage, based on an estimate of 12 units per total human immunizing dose, as the unitage of the corresponding dilution of the standard vaccine. Each mouse in each group for vaccination shall be injected intraperitoneally with 0.5 ml. of the appropriate dilution.

(2) The interval between vaccination and challenge shall be 14 to 17 days. At least 87.5 percent of the mice in each group shall survive the period between vaccination and challenge and each mouse challenged shall appear healthy.

(c) *The challenge.* (1) The challenge culture of *Bordetella pertussis* for each test shall be taken from a batch of cultures which have been maintained by a method, such as freeze-drying, that retains constancy of virulence.

(2) The challenge and virulence titration doses shall be prepared as follows: The bacteria shall be harvested from a 20 to 24 hour culture grown on Bordet-Gengou medium seeded from a rapidly growing culture less than 48 hours old and uniformly suspended in a solution containing 1.0 percent casein peptone and about 0.6 percent sodium chloride at pH 7.1±0.1. The suspension, freed from agar particles and clumps of bacteria, and adjusted to an opacity of 10 units, shall be diluted in the solution used for suspending the bacteria, to provide in a volume of 0.03 ml. (i) a challenge dose of 0.0001 opacity units (1:3000) and (ii) virulence titration doses of $^1/_{50}$, $^1/_{250}$ and $^1/_{1250}$ respectively of the challenge dose.

(3) Each vaccinated mouse shall be injected intracerebrally with the challenge dose. The four groups of control mice shall be injected intracerebrally with the challenge dose and its three dilutions, respectively. The challenge-dose control mice shall be injected last. The interval between the removal of the bacteria from the culture medium and the injection of the last mouse shall not exceed 2½ hours.

(d) *Recording the results.* The mice shall be observed for 14 days. Mice dying within 72 hours after challenge shall be excluded from the test. Records shall be maintained of the number of mice that die after 72 hours and of the number of mice showing both paralysis and enlargement of the head at the end of 14 days. All mice that show both paralysis and enlargement of the head shall be considered as deaths for the purposes of determining the ED_{50}.

(e) *Validity of the test.* The test shall be valid provided (1) the ED_{50} of the vaccine under test and the standard vaccine is between the largest and smallest vaccinating doses; (2) the limits of one standard deviation of each ED_{50} fall within the range of 64 percent to 156 percent; (3) the protective response is graded in relation to the vaccinating doses; (4) the dose-response curves of the vaccine under test and the standard vaccine are parallel; (5) the challenge dose contains approximately 200 LD_{50}; (6) the LD_{50} contains no more than 300 colony forming units; and (7) the $^1/_{1250}$ dilution of the challenge dose contains no less than 10 and no more than 50 colony forming units.

(f) *Estimate of the potency.* The ED_{50} of each vaccine shall be calculated by a

method that provides an estimate of the standard deviation. The protective unit value per total human immunizing dose of the vaccine under test shall be calculated in terms of the unit value of the standard vaccine.

(g) *Potency requirements.* The vaccine shall have a potency of 12 units per total human immunizing dose based upon either a single test estimate of no less than 8 units or a two-, three- or four-test geometric mean estimate of no less than 9.6, 10.8, or 12 units, respectively, except that for the vaccine in a multiple antigen product containing Poliovirus Vaccine Inactivated, the estimate shall be no less than 14 units. In no event shall the estimate be more than 36 units.

(h) *Test design variation.* Variations in the design of the potency test may be permitted providing the results are demonstrated to be of equal or greater precision.

[38 FR 32064, Nov. 20, 1973, as amended at 50 FR 4137, Jan. 29, 1985]

§ 620.5 Mouse toxicity test.

The final vaccine shall be demonstrated to be free from toxicity by the following test:

A group of no less than 10 mice, each mouse weighing 14 to 16 grams, shall have free access to food and water for no less than 2 hours before injection. The group weight of the mice shall be determined immediately prior to injection. Each mouse shall be injected intraperitoneally with a test dose of one-half of the largest recommended single human dose of the final vaccine in a volume of no less than 0.5 ml. nor more than 0.75 ml. The group weight of the mice shall be determined at the end of 72 hours and at the end of 7 days after injection. At the end of 72 hours the average weight per mouse may be no less than the average weight per mouse immediately preceding the injection; at the end of 7 days the average weight gain per mouse may be no less than 3.0 grams; and at the end of 7 days there may be vaccine-related deaths of no more than 5 percent of the total number of mice in all the toxicity tests performed.

§ 620.6 General requirements.

(a) *Safety.* Each lot of product containing Pertussis Vaccine shall be tested for safety by the procedures prescribed in § 610.11 of this chapter except that the test shall consist of the intraperitoneal injection of no less than one-half of the recommended largest individual human dose into each of the mice, and either the intraperitoneal injection of no less than three times the recommended largest individual human dose, or the subcutaneous injection of 5.0 milliliters into each of the guinea pigs.

(b) *Dose.* These additional standards are based on a single injection of 0.5 ml., 1.0 ml., or 1.5 ml., and a total human immunizing dose of three single injections of a nonadsorbed vaccine, and two or three single injections of an adsorbed vaccine.

(c) *Product characteristics.* Recommendations shall be made through appropriate labeling that the product after issue should not be frozen and should be well shaken immediately prior to use.

(d) *Labeling.* In addition to the items required by other applicable labeling provisions of this part, the package label shall give the following information:

(1) For a vaccine containing a precipitant or an adsorbent, the word ''Adsorbed'' shall follow the proper name in the same style of type and prominence as the proper name.

(2) The total immunizing dose contains 12 units of pertussis vaccine.

(e) *Multiple antigen products.* The Pertussis Vaccine components of multiple antigen products shall be manufactured pursuant to these additional standards, except that the mouse toxicity test (§ 620.5) and the potency test (§ 620.4) shall be performed on the multiple antigen product.

(f) *Adsorbed vaccines.* Only aluminum compound reagents shall be introduced into the product to cause precipitation or adsorption of either Pertussis Vaccine or other antigens incorporated with Pertussis Vaccine.

(g) *Freezing prohibition.* Pertussis Vaccine and multiple antigen products of which Pertussis Vaccine is a component shall not be frozen at any time during storage.

(h) *Samples and protocols.* For each lot of vaccine, the following material shall be submitted to the Director, Center for Biologics Evaluation and Research, Food and Drug Administration, 8800 Rockville Pike, Bethesda, MD 20892.

(1) A sample of no less than 20 milliliters of the final product for pertussis vaccine testing.

(2) Protocols showing summaries of the manufacturing processes and the results of all mouse toxicity (§ 620.5) and potency (§ 620.4) tests performed.

[38 FR 32064, Nov. 20, 1973, as amended at 41 FR 35480, Aug. 23, 1976; 48 FR 13025, Mar. 29, 1983; 49 FR 23834, June 8, 1984; 51 FR 15610, Apr. 25, 1986; 55 FR 11013, Mar. 26, 1990]

Subpart B—Typhoid Vaccine

§ 620.10 Typhoid Vaccine.

The proper name of this product shall be Typhoid Vaccine which shall be an aqueous or dried preparation of killed *Salmonella typhi* bacteria.

[48 FR 7167, Feb. 18, 1983]

§ 620.11 Production.

(a) *Strain of bacteria.* (1) Strain Ty 2 of *Salmonella typhi* shall be used in the manufacture of Typhoid Vaccine.

(2) The antigenic integrity of the Ty 2 strain shall be verified by an appropriate serological procedure.

(b) *Propagation of bacteria.* The culture medium for propagation of *S. typhi* shall not contain ingredients known to be capable of producing allergenic effects in human subjects. The harvested bacteria shall be free of extraneous bacteria, fungi, and yeasts, as demonstrated by microscopic examination and cultural methods.

(c) *Bacterial content.* (1) The number of bacteria in the concentrate of harvested bacteria shall be estimated not later than 2 weeks after harvest and before any treatment capable of altering the accuracy of the estimate.

(2) The number of *S. typhi* bacteria in the vaccine shall not exceed 10^9 per milliliter.

(d) *Nitrogen content.* The total nitrogen content of the vaccine shall not exceed 0.035 mg./ml. for nonextracted bacteria preparations and shall not exceed 0.023 mg./ml. for acetone-extracted bacteria preparations.

(e) *Preservative.* Aqueous vaccine and the solution for reconstitution supplied with dried vaccine shall contain a preservative. Dried vaccine shall not contain a preservative.

[38 FR 32064, Nov. 20, 1973, as amended at 48 FR 7167, Feb. 18, 1983]

§ 620.12 U.S. Standard preparations.

The following U.S. Standard preparations shall be obtained from the Center for Biologics Evaluation and Research (HFB–210), Food and Drug Administration, 8800 Rockville Pike, Bethesda, MD 20892, for use as prescribed in this part:

(a) *Vaccine standard.* The U.S. Standard Typhoid Vaccine for determining the potency of Typhoid Vaccine.

(b) *Opacity standard.* The U.S. Opacity Standard for adjusting the opacity of the suspension from which the challenge culture is prepared.

[48 FR 7167, Feb. 18, 1983, as amended at 49 FR 23834, June 8, 1984; 51 FR 15610, Apr. 25, 1986; 55 FR 11015, Mar. 26, 1990]

§ 620.13 Potency test.

The number of potency units per milliliter shall be estimated for each lot of vaccine from the results of simultaneous mouse protection tests of the vaccine under test and of the U.S. Standard Typhoid Vaccine. At least four dilutions of each lot of vaccine shall be tested. The test shall be performed as follows:

(a) *Mice.* Healthy mice shall be used, all from a single strain and of the same sex, or an equal number of each sex in each group, with individual weights between 13 and 16 grams. A system of randomization shall be used to distribute the mice into the groups, with respect to shelf position and to determine the order of challenge. A group of at least 16 mice shall be used for each dilution of each vaccine. There shall be at least 4 groups consisting of no less than 10 mice each for control testing purposes, as required under paragraph (c) of this section.

(b) *Inoculation of vaccine.* (1) Serial dilutions, no greater than fivefold, of the vaccine to be tested and of the standard vaccine shall be made in saline (0.85 percent sodium chloride solution or phosphate-buffered saline). The mean

effective dose (ED_{50}) value shall be bracketed by the dilutions used. Each mouse in each group for inoculation shall be injected intraperitoneally with 0.5 milliliter of the appropriate dilution.

(2) The interval between inoculation of the vaccine and challenge shall be no less than 7 days nor more than 14 days. At least 87.5 percent of the mice in each group shall survive the period between vaccine inoculation and challenge and each mouse challenged shall appear healthy.

(c) *The challenge.* (1) The challenge culture of Strain Ty 2 of *S. typhi* for each test shall be taken from a batch of cultures maintained by a method, such as freeze-drying, that retains constancy of virulence.

(2) The challenge and virulence titration doses shall be prepared as follows: The bacteria shall be harvested from a 5- to 6-hour culture grown at 36°±1° C on a suitable agar medium that shall have been seeded from a 16- to 20-hour culture grown at 36°±1° C on a suitable agar medium, and the harvested bacteria then shall be uniformly suspended in saline or phosphate-buffered saline. The suspension, freed from agar particles and clumps of bacteria and adjusted to an opacity of 10 units, shall be diluted in saline or phosphate-buffered saline by tenfold increments. The suspensions for the challenge and virulence titration doses shall be put into a sterile gastric mucin preparation or other suitable virulence-enhancing preparation. The challenge suspension shall be prepared from whichever bacteria dilution provides about 1,000 colony forming units for a 0.5 milliliter challenge dose. The virulence titration suspensions shall be 10^1, 10^2, 10^3 dilutions, respectively, of the challenge suspension.

(3) Each mouse inoculated with vaccine shall be injected intraperitoneally with an 0.5 ml. dose of the challenge suspension. Each mouse in the four groups of control mice shall be injected intraperitoneally with an 0.5 ml. dose of the challenge suspension and its three dilutions, respectively. The challenge dose control mice shall be injected last. The interval between removal of the bacteria from the culture medium and the injection of the last mouse shall not exceed 2½ hours.

(d) *Recording the results.* The mice shall be observed daily for 3 days. A record shall be maintained of the number of mice that die. A record of the number of mice that survive shall be made at the end of the observation period.

(e) *Validity of the test.* The test is deemed valid if: (1) The ED_{50} of the vaccine under test and the standard vaccine is between the largest and smallest doses inoculated into the mice;

(2) The homogeneity of the dose response lines for both the vaccine under test and the standard vaccine is acceptable;

(3) A graded protective response is obtained in relation to the vaccine dilutions;

(4) The slopes of the dose response curves for the vaccine under test and the standard vaccine are shown to be parallel by an appropriate statistical method;

(5) The results of all dilutions are used to calculate the ED_{50} value of both the standard and test vaccine by a parallel line bioassay method or a statistically equivalent method;

(6) The challenge dose contains approximately 1,000 colony forming units; and

(7) The LD_{50} of the challenge dose contains no more than 20 colony forming units.

(f) *Repeat tests.* If the test does not meet the criteria prescribed in paragraph (e) of this section, repeat tests may be performed. The results of all tests shall be combined by geometric mean. Any test result established as invalid under §610.1 of this chapter may be disregarded. The determination that the vaccine meets the potency requirements shall be made from the results of not more than four valid tests.

(g) *Estimate of the potency.* The ED_{50} of each vaccine shall be calculated. The protective unit value per milliliter of the vaccine under test shall be calculated in terms of the unit value of the standard vaccine.

(h) *Potency requirements.* The results of at least two separate tests shall be included on the release protocol, required under §620.14(c)(2), that is submitted to the Center for Biologics

Evaluation and Research, Food and Drug Administration. The vaccine shall have a potency of 8.0 units per milliliter. This requirement shall be met only if the geometric mean potency for two tests is not less than 3.9 units per milliliter; or for three tests, not less than 4.4 units per milliliter; or for four tests, not less than 4.8 units per milliliter.

[38 FR 32064, Nov. 20, 1973, as amended at 48 FR 7167, Feb. 18, 1983; 49 FR 23834, June 8, 1984; 55 FR 11013, Mar. 26, 1990]

§ 620.14 General requirements.

(a) *Dose.* These standards are based on a human adult dose of 0.5 ml. for a single injection and a total immunizing dose of two injections of 0.5 ml. given at appropriate intervals.

(b) *Labeling.* In addition to the items required by other applicable labeling provisions of this subchapter, the package label shall state that the vaccine contains 8 units per milliliter.

(c) *Samples; protocols; official release.* For each lot of vaccine, the following material shall be submitted to the Director, Center for Biologics Evaluation and Research (HFB–1), 8800 Rockville Pike, Bethesda MD 20892.

(1) A sample of no less than 40 ml. of the product distributed in no less than four containers.

(2) A protocol that consists of a summary of the history of manufacture of each lot including all results of each test for which test results are requested by the Director, Center for Biologics Evaluation and Research.

(3) The product shall not be issued by the manufacturer until written notification of official release of each filling lot of dried vaccine and of each bulk lot of aqueous vaccine is received from the Director, Center for Biologics Evaluation and Research.

[38 FR 32064, Nov. 20, 1973, as amended at 42 FR 27582, May 31, 1977; 48 FR 7168, Feb. 18, 1983; 48 FR 11430, Mar. 18, 1983; 49 FR 23834, June 8, 1984; 51 FR 15610, Apr. 25, 1986; 55 FR 11013 and 11015, Mar. 26, 1990]

Subpart C—Anthrax Vaccine Adsorbed

§ 620.20 Anthrax Vaccine Adsorbed.

The proper name of this product shall be Anthrax Vaccine Adsorbed, which shall consist of an aqueous preparation of a fraction of *Bacillus anthracis* which contains the protective antigen adsorbed on aluminum hydroxide.

[38 FR 32064, Nov. 20, 1973, as amended at 50 FR 4137, Jan. 29, 1985]

§ 620.21 Production.

(a) *Strain of bacteria.* A nonencapsulated, nonproteolytic, avirulent strain of *Bacillus anthracis* shall be used in the manufacture of anthrax vaccine.

(b) *Medium.* A chemically defined medium shall be used for the propagation of *Bacillus anthracis* which has protective-antigen promoting properties that are no less effective than the protective-antigen promoting properties of the Puziss and Wright 1095 medium as set forth in U.S. Patent No. 3,208,909, issued September 28, 1965, which patent is hereby incorporated by reference and deemed published herein. U.S. Patent No. 3,208,909 has been assigned to the Federal Government and copies will be provided to persons affected by the provisions of this subchapter upon request to the Director, Center for Biologics Evaluation and Research, or to the appropriate Information Center Officer listed in 45 CFR, part 5. Copies also may be obtained upon request from the U.S. Patent Office, Washington, DC. The medium shall not contain ingredients known to be capable of producing allergenic effects in human subjects.

(c) *Propagation of bacteria.* The medium shall be inoculated with a 24-hour old vegetative culture seeded from a stock suspension of spores. The propagation culture, flushed with nitrogen, shall be incubated at 37° C.±1.0° C., agitated for approximately 27 hours, cooled to about 20° C., the pH adjusted to 8.0±0.1 and then filtered through a sterilizing filter(s) using nitrogen gas under pressure.

(d) *Adsorption of the protective antigen.* The sterile filtrate shall be adsorbed on sterile aluminum hydroxide gel and the recovered precipitate shall be resuspended and diluted in sterile 0.85 percent sodium chloride solution.

[38 FR 32064, Nov. 20, 1973, as amended at 49 FR 23834, June 8, 1984; 55 FR 11013, Mar. 26, 1990]

§ 620.22 U.S. Reference preparation.

The U.S. Reference Anthrax Vaccine distributed by the Center for Biologics Evaluation and Research shall be used for determining the potency of anthrax vaccine.

[38 FR 32064, Nov. 20, 1973, as amended at 49 FR 23834, June 8, 1984; 55 FR 11013, Mar. 26, 1990]

§ 620.23 Potency test.

The potency of each lot of vaccine shall be estimated from the results of simultaneous tests of the vaccine under test and the U.S. Reference Anthrax Vaccine. The test shall be performed as follows:

(a) *Guinea pigs.* Healthy guinea pigs shall be used, all from a single strain and of the same sex, or an equal number of each sex in each group, with individual weights between 325 and 350 grams. The diet of the guinea pigs shall be supplemented with vitamin C throughout the test period. At least three groups of no less than eight guinea pigs shall be used for each vaccine and at least one group of four guinea pigs shall be used for the challenge control.

(b) *Vaccination.* Serial dilutions, not greater than three-fold, of each vaccine shall be made in 0.85 percent sodium chloride solution. The mid-dilution of the vaccine under test shall contain that amount of vaccine which will afford protection to approximately 50 percent of the guinea pigs in the group vaccinated with that dilution. Each guinea pig in the test and reference vaccine groups shall be injected subcutaneously with 0.5 ml. of the appropriate dilution on the left side of the abdomen and about 2 cm. from the midline. The interval between vaccination and challenge shall be 14 days.

(c) *The challenge.* Each vaccinated and control guinea pig shall be injected intracutaneously on the right side of the abdomen with 0.1 ml. of a spore suspension of the virulent Vollum strain of *Bacillus anthracis* diluted in sterile distilled water to contain 10,000 spores per milliliter.

(d) *Recording the results.* The guinea pigs shall be observed daily for 10 days and the deaths recorded. The number of survivors shall be recorded at the end of the observation period.

(e) *Validity of the test.* The test shall be valid provided (1) the protective response to each vaccine is graded in relation to the amount of vaccine in the respective dilutions and (2) all control animals die within 10 days.

(f) *Potency requirement.* The potency of the product is satisfactory if the vaccine is no less potent than the reference. The potency of the product is considered to be equal to the reference when (1) the average time of death of the product-vaccinated guinea pigs is no less than the average time of death of the reference-vaccinated guinea pigs and the number of survivors of the product-vaccinated guinea pigs is no less than the number of survivors of the reference-vaccinated guinea pigs, or (2) the use of another statistical procedure, shown to be adequate for evaluating the potency of anthrax vaccine, demonstrates that the product is no less potent than the reference.

§ 620.24 General requirements.

(a) *Dose.* These standards are based on a single human dose of 0.5 ml. and a total primary immunizing doses of three single doses, each given at appropriate intervals.

(b) *Product characteristics.* Recommendation shall be made through appropriate labeling that the product after issue should not be frozen.

(c) *Samples; protocols; official release.* For each lot of vaccine, the following material shall be submitted to the Director, Center for Biologics Evaluation and Research, Food and Drug Administration, 8800 Rockville Pike, Bethesda, MD 20892:

(1) A protocol which consists of a summary of the manufacture of each lot including all results of all tests for which test results are requested by the Director, Center for Biologics Evaluation and Research.

(2) A sample of no less than 40 milliliters of the final product distributed in approximately equal amounts into four final containers.

(3) The product shall not be issued by the manufacturer until written notification of official release of the lot is received from the Director, Center for Biologics Evaluation and Research.

[38 FR 32064, Nov. 20, 1973, as amended at 42 FR 27582, May 31, 1977; 48 FR 13025, Mar. 29, 1983; 49 FR 23834, June 8, 1984; 51 FR 15610, Apr. 25, 1986; 55 FR 11013, Mar. 26, 1990]

Subpart D—Cholera Vaccine

§ 620.30 Cholera Vaccine.

The proper name of this product shall be Cholera Vaccine, which shall consist of an aqueous preparation of equal parts of Ogawa and Inaba serotypes of killed *Vibrio cholerae* bacteria.

[41 FR 18295, May 3, 1976]

§ 620.31 Production.

(a) *Strains of bacteria.* (1) A strain of Ogawa and a strain of Inaba serotypes of *V. cholerae* shall be used in the manufacture of the vaccine. Each serotype strain shall have been shown in controlled field studies to yield a vaccine no less potent than vaccines prepared from Ogawa strain 41 and Inaba strain 35A3 obtained from the Center for Biologics Evaluation and Research.

(2) Antigenic integrity of the strains shall be verified by (i) the agglutination of living bacteria of each serotype by cholera O Group I antiserum; (ii) the agglutination of the Ogawa strain in monospecific Ogawa antiserum and of the Inaba strain in monospecific Inaba antiserum; and (iii) the absence of spontaneous agglutination of living bacteria of either strain in 0.85 percent sodium chloride solution during incubation for at least 5 hours at 37° C.

(b) *Propagation of bacteria.* The culture medium for the propagation strains shall not contain ingredients known to be capable of producing allergenic effects in human subjects. The harvested bacteria shall be free of extraneous bacteria, fungi, and yeasts as demonstrated by microscopic examination and cultural methods. Bacteria of the two serotypes shall be grown separately.

(c) *Bacterial content.* (1) The number of bacteria in each separate bacterial harvest shall be determined by use of the U.S. Opacity Standard not later than 2 hours after harvest and before treatment with a preservative or other agent capable of altering opacity of the bacterial suspension.

(2) The vaccine shall contain equal numbers of bacteria of the Ogawa and Inaba serotypes, and the total number shall not exceed 8×10^9 bacteria per milliliter.

(d) *Nitrogen content.* The total nitrogen content of the vaccine shall not exceed 0.3 milligram per milliliter for bacteria grown on solid medium or 1.0 milligram per milliliter if grown in liquid medium. In no instance shall the vaccine contain more than 0.07 milligram per milliliter of nitrogen precipitable by the addition of an equal volume of 10 percent trichloracetic acid.

(e) *Preservative.* The vaccine shall contain a preservative.

[41 FR 18295, May 3, 1976, as amended at 49 FR 23834, June 8, 1984; 55 FR 11013, Mar. 26, 1990]

§ 620.32 U.S. Standard preparations.

The following U.S. Standard preparations shall be obtained from the Center for Biologics Evaluation and Research, Food and Drug Administration, for use as prescribed in this subpart:

(a) *Vaccine standard.* The U.S. Standard Cholera Vaccine, Ogawa serotype, and U.S. Standard Cholera Vaccine, Inaba serotype, shall be reconstituted as directed for determining the potency of Cholera Vaccine.

(b) *Opacity standard.* The U.S. Opacity Standard for use in estimating the bacterial content of the vaccine and of the challenge culture.

(c) *Seed culture.* Seed cultures of *V. cholerae,* Inaba serotype, strain 35A3 and Ogawa serotype, strain 41, for preparation of vaccine challenge cultures for use in the vaccine potency test.

[41 FR 18295, May 3, 1976, as amended at 49 FR 23834, June 8, 1984; 55 FR 11013, Mar. 26, 1990]

§ 620.33 Potency tests.

Each lot of vaccine shall be subjected to two potency tests. One test shall determine the potency of the vaccine in comparison with the U.S. Standard

Cholera Vaccine, Ogawa serotype, and the other test shall determine the potency of the vaccine in comparison with the U.S. Standard Cholera Vaccine, Inaba serotype. At least four dilutions of each vaccine shall be tested. Each test shall be performed as follows:

(a) *Mice.* Healthy mice shall be used, all from a single strain and of the same sex, or an equal number of each sex in each group, with individual weights between 10 and 14 grams. A group of at least 16 mice shall be used for each dilution of each vaccine. In addition, there shall be at least 4 groups consisting of no less than 10 mice each for each potency test as a control for virulence titration of the challenge suspension.

(b) *Injections of vaccine.* Serial dilutions, no greater than fivefold, of the vaccine to be tested and of the appropriate serotype standard vaccine shall be made in 0.85 percent sodium chloride solution. The median effective dose (ED_{50}), which is the dose of vaccine that is expected to protect 50 percent of the animals that received the vaccine, shall be bracketed by the dilutions used. Each mouse in each dilution group shall receive intraperitoneally 0.5 milliliter of the appropriate vaccine dilution. At least 87.5 percent of the mice in each dilution group shall survive, and all surviving mice shall appear healthy at the time of challenge.

(c) *The challenge.* The challenge shall be administered 12 to 16 days after injection of the vaccine.

(1) The strains of *V. cholerae* for challenge shall be Ogawa 41 and Inaba 35A3, except that *V. cholerae,* Inaba serotype, strain V86 may be used instead of Inaba serotype, strain 35A3, for preparation of vaccine challenge culture: *Provided,* That the source of the challenge culture shall be identified and verified by the manufacturer as equal to that distributed by the World Health Organization. For each test, the challenge culture shall be taken from a batch of cultures maintained by a method such as freeze-drying that retains constancy of virulence.

(2) The challenge and virulence titration doses shall be prepared as follows: The bacteria for each challenge shall be harvested from a 6- to 18-hour culture grown at 36°±1° C, on a suitable agar medium adjusted to pH 7.4. The harvested bacteria shall be uniformly suspended in a diluent consisting of M/15 phosphate buffered saline adjusted to pH 7.4 and shall contain 0.1 to 0.2 percent gelatin. The suspension shall be free from agar particles and clumps of bacteria. The suspension shall be adjusted to an opacity of 10 units, and diluted in tenfold increments using the same diluent. The suspensions for the challenge and virulence titrations shall be suspended in a 5 to 10 percent sterile gastric mucin preparation adjusted to pH 7.4. The challenge suspension shall be prepared from whichever bacterial dilution provides the required median lethal dose (LD_{50}) for a 0.5 milliliter challenge dose. The LD_{50} is the dose of the challenge suspension that is expected to kill 50 percent of the animals that received the challenge. The virulence titration suspensions shall consist of the challenge suspension and at least three dilutions of the challenge suspension calculated to bracket the LD_{50} value.

(3) At least 16 surviving mice, randomly selected from each dilution group that received vaccine, shall be inoculated intraperitoneally with a 0.5-milliliter dose of the challenge suspension. Mice in each of the four groups of control mice used for the virulence titration of the challenge suspension shall be inoculated intraperitoneally with a 0.5-milliliter dose of the challenge suspension and its respective dilutions. The challenge dose control mice shall be inoculated last. The interval between removal of the bacteria from the culture medium and the inoculation of the last mouse shall not exceed 2½ hours.

(d) *Recording the results.* The mice shall be observed daily for 2 days following challenge. A daily record shall be maintained of the number of mice that die. A record of the number of mice that survive shall be made at the end of the observation period.

(e) *Validity of the test.* The test is valid provided: (1) The ED_{50} value of the vaccine under test and the standard vaccine is between the largest and smallest doses inoculated into the mice;

(2) The homogeneity of the dose response lines for both the vaccine under test and the standard vaccine is acceptable;

(3) The log-dose response lines for the vaccine under test and the standard vaccine are shown to be parallel by an appropriate statistical method;

(4) The results of all dilutions shall be used to calculate the ED_{50} value of both the standard and test vaccine by a parallel line bioassay method or a method statistically equivalent;

(5) The challenge dose contains between 100 and 10,000 LD_{50} doses; and

(6) The LD_{50} value of the challenge suspension contains no more than 10,000 colony-forming units determined by plate count.

(f) *Repeat tests.* Repeat tests need be performed only on the serotype which failed to meet the potency requirements prescribed in paragraph (h) of this section. The results of each test on each serotype meeting the criteria in paragraph (e) of this section shall be combined by means of a geometric mean. The determination that the vaccine meets the potency requirements shall be made from the results of not more than three valid tests on each serotype.

(g) *Estimate of the potency.* The ED_{50} value of each vaccine shall be calculated. The protective unit value of each serotype per milliliter of the vaccine under test shall be calculated in terms of the unit value of the corresponding standard vaccine.

(h) *Potency requirements.* The vaccine shall have a potency of not less than 8 units per serotype per milliliter. This requirement shall be met only if the potency for a single test is not less than 4.4 units per serotype per milliliter, or for two tests not less than 5.3 units, or for three tests not less than 5.7 units.

[41 FR 18295, May 3, 1976, as amended at 41 FR 46587, Oct. 22, 1976]

§ 620.34 Mouse toxicity test.

The final vaccine shall be demonstrated to be free from toxicity by the following test: A group of no less than 10 and no more than 40 mice, each mouse weighing 14 to 16 grams, shall have free access to food and water at least 2 hours before injection and throughout the test period. The group weight of the mice shall be determined immediately before injection. Each mouse shall be injected intraperitoneally with a test dose of 0.5 milliliter of undiluted vaccine. The group weight of the mice shall be determined again at the end of 72 hours. The 72-hour average weight per mouse shall be no less than the average weight per mouse immediately preceding the injection. No more than 5 percent of the total number of mice used may die during the test period; however, neither death nor significant toxic signs attributable to the vaccine shall result.

[41 FR 18295, May 3, 1976]

§ 620.35 General requirements.

(a) *Freezing prohibition.* Cholera Vaccine shall not be frozen at any time.

(b) *Dose.* These standards are based on a total immunizing dose of two injections of 0.5 milliliter and 1.0 milliliter, respectively, given at intervals specified in the manufacturer's labeling.

(c) *Date of manufacture.* The date of manufacture shall be the date of initiation of the last valid potency test for the Ogawa serotype or the Inaba serotype, whichever date is earlier.

(d) *Labeling.* In addition to the applicable labeling provisions of this chapter, the package label shall bear the following: (1) A statement that the vaccine contains 8 units of each serotype antigen per milliliter.

(2) The statement, ''DO NOT FREEZE''.

(3) The statement, ''SHAKE WELL''.

(e) *Samples; protocols; official release.* For each lot of vaccine, the following material shall be submitted to the Director, Center for Biologics Evaluation and Research, Food and Drug Administration, 8800 Rockville Pike, Bethesda, MD 20892.

(1) A sample consisting of no less than 40 milliliters of the product. The sample may be in the final container or from the vaccine bulk lot.

(2) A protocol which consists of a summary of the history of manufacture of each lot including all results of each test for which test results are requested by the Director, Center for Biologics Evaluation and Research,

Food and Drug Administration. The raw data and results from each potency test performed shall be included.

(3) The product shall not be issued by the manufacturer until written notification of official release of the lot is received from the Director, Center for Biologics Evaluation and Research.

[41 FR 18295, May 3, 1976, as amended at 42 FR 27582, May 31, 1977; 49 FR 23834, June 8, 1984; 51 FR 15610, Apr. 25, 1986; 55 FR 11013, Mar. 26, 1990]

Subpart E—Bacillus of Calmette and Guerin (BCG) Vaccine

SOURCE: 44 FR 14545, Mar. 13, 1979, unless otherwise noted.

§620.40 BCG Vaccine.

(a) *Proper name and definition.* The proper name of this product is BCG Vaccine. The product is defined as a freeze-dried preparation containing viable bacteria of the Bacillus of Calmette and Guerin, which is an attenuated strain of *Mycobacterium bovis.*

(b) *Criteria for an acceptable strain.* The source of the BCG strain used in the manufacture of any lot of the final product must be identified by complete historical records.

(1) *Seed lot system.* The BCG strain must be maintained in the form of a primary seed lot that is to be the basic material from which all secondary seed lots are prepared. Production of BCG Vaccine may be from either primary or secondary seed lots. Each seed lot must be stored in either a freeze-dried state at −20° C or colder, or in a frozen state at −70° C or colder.

(2) *Freedom from virulence.* The BCG strain is demonstrated to be incapable of producing progressive tuberculosis in guinea pigs tested as prescribed in §620.45, except that no fewer than 48 guinea pigs must be used to test the primary seed lot and no fewer than 12 guinea pigs must be used to test each secondary seed lot. At least two-thirds of the animals must survive the observation period of no less than 6 months.

(3) *Induction of tuberculin sensitivity in guinea pigs.* Each of at least 10 guinea pigs is to be injected with 1 human dose of BCG Vaccine and, within 4 to 6 weeks after vaccination, skin tested with tuberculin. At least 80 percent of the guinea pigs tested must develop tuberculin sensitivity, as prescribed in §620.44(b)(3)(ii).

(4) *Clinical information.* Clinical data must establish that the BCG strain is safe and induces tuberculin sensitivity. After having passed all laboratory tests prescribed for BCG Vaccine, each primary and secondary seed lot of vaccine must be tested for its ability to induce sensitivity in tuberculin-negative persons. Only those persons tested by injection of 5 U.S. Tuberculin Units, Purified Protein Derivative, by the Mantoux technique and found negative in this test are to be selected for clinical trials. At least 100 tuberculin-negative persons must be included in the test of the primary seed lot, and at least 20 tuberculin-negative persons must be included in the test of each secondary seed lot. Within 6 to 8 weeks after BCG vaccination, the vaccinees must be tested for tuberculin reactivity by injecting not more than 10 U.S. Tuberculin Units, Purified Protein Derivative, by the Mantoux technique. The test is considered satisfactory if a least 90 percent of those persons from each group develop tuberculin reactivity as indicated by an induration reaction of at least 5 millimeters in diameter.

§620.41 Establishment and personnel requirements.

In addition to the applicable requirements of §§600.10 and 600.11 of this chapter, the following practices and procedures are required:

(a) *Isolation of BCG unit.* (1) A BCG unit is defined as the space used for storage of primary and secondary seed cultures and for vaccine preparation, including culture maintenance, media inoculation for propagation, harvesting, filling into final containers, sealing of final containers, media production, and cleaning and sterilization of glassware. For purposes of these additional standards, the space used for incubation of bulk and final container sterility tests, tests to determine the numbers of colony-forming units, animal tests, and necropsies are not part of the BCG unit.

(2) The BCG unit must be completely isolated from other production and surrounding areas and must be situated

and designed to prevent contamination of the product. It must have a separate facility for ventilation, designed to prevent contamination of the product. The facilities for water supply and sewage and trash disposal must be designed to prevent microbial contamination of the BCG unit. The equipment used in BCG Vaccine production must remain in the BCG unit at all times.

(3) Microbial controlled areas must be available for handling the BCG cultures. No cultures of microorganisms other than the BCG production strain are permitted in the BCG unit. No animals are permitted in the BCG unit. All tests necessary for the control of the vaccine, in which contaminating microorganisms may be cultured, or in which animals are used, must be conducted in space physically separated from the BCG unit.

(b) *Restrictions on personnel.* (1) A staff specially trained in maintaining the seed cultures, propagating the cultures, preparing the vaccine, and filling the vaccine into final containers shall be employed in the production of the BCG Vaccine. Such personnel shall not work with other infectious agents in any laboratory at any time and shall not be exposed to a known risk of tuberculosis. Within 30 days before employment in the BCG unit, each person working in the unit shall have had a medical examination, including a tuberculin skin test with 5 U.S. Tuberculin Units, Purified Protein Derivative, by the Mantoux procedure, and a chest X-ray. No person who has had a history of tuberculosis or mycobacterial disease is permitted in the BCG unit. There must be periodic medical examinations of BCG unit personnel, including X-ray examinations, of sufficient frequency to detect the appearance of early active tuberculosis. Repeated tuberculin skin testing of staff who are negative to tuberculin may be used as an additional diagnostic aid in isolating any potential source of tuberculosis exposure. If a person working in the BCG unit develops active tuberculosis, (i) the entire staff shall be examined for possible tuberculosis infection, (ii) all current vaccine preparations and all cultures with which the person may have come into contact since his or her last satisfactory medical examination, except cultures sealed before that examination, must be discarded, and (iii) the BCG unit and all equipment with which the person may have come in contact must be decontaminated.

(2) Personnel shall wear protective clothing and use protective devices to the extent necessary to protect the product from contamination.

(3) Any person not assigned to the BCG unit shall not be allowed into the BCG unit at any time unless a medical examination shows the person to be free from mycobacterial disease.

§ 620.42 Production.

(a) *BCG inoculum.* The inoculum of BCG used for seed lot or production of final lot in seed buildup must have been removed from the preceding seed lot in accordance with the following passage and time schedule:

(1) No more than 3 passages from primary to secondary seed lot within a 2-month period.

(2) If no secondary seed lot is used, no more than 9 passages from primary seed lot to final lot within a 6-month period.

(3) No more than 9 passages from secondary seed lot to final lot within a 6-month period.

(b) *Propagation of bacteria.* The culture medium for propagation of BCG Vaccine must not contain ingredients known to be capable of producing allergenic effects in humans or of causing the bacteria to become virulent for guinea pigs. The growth in each container must be examined visually, and only those cultures that have the typical growth pattern characteristic of BCG are to be used in a vaccine.

(c) *Colony-forming units (CFU) before and after freeze-drying.* Each lot of BCG Vaccine must be tested to determine the number of CFU per individual final container both before and after freeze-drying, by the method prescribed in § 620.44(a). The upper and lower limits of the viable count are to be established by the manufacturer of the vaccine for the particular route of administration recommended and must be specified in the license application. The loss in viability after drying must not exceed 90 percent.

§ 620.43 Reference BCG Vaccine.

A reference BCG Vaccine, for use in determining the validity of the test for colony-forming units, is to be obtained from the Director, Center for Biologics Evaluation and Research, Food and Drug Administration, 8800 Rockville Pike, Bethesda, MD 20892.

[44 FR 14545, Mar. 13, 1979, as amended at 49 FR 23834, June 8, 1984; 51 FR 15610, Apr. 25, 1986; 55 FR 11013, Mar. 26, 1990]

§ 620.44 Potency tests.

(a) *Colony-forming units (CFU).* The number of CFU must be determined on the contents of each of at least 10 individual final containers of each lot of BCG Vaccine. Of the 10 or more individual final containers, the contents of at least 5 before, and an equal number after, freeze-drying must be tested. Final containers of the freeze-dried vaccine are to be reconstituted as for human use with the diluent recommended by the manufacturer. The number of CFU to be reported for each lot of BCG Vaccine must be determined only from test tubes containing between 10 and 50 CFU. Dilutions must be made as follows:

(1) Dilutions are made from an appropriate volume of the liquid vaccine before freeze-drying or the reconstituted vaccine after freeze-drying. Appropriate dilutions are made with modified Youman's medium specified in paragraph (a)(4) of this section, up to a point where subsequent serial half-log dilutions will result in at least 1 tube containing between 10 and 50 CFU.

(2) Serial half-log dilutions are made in 16×125 millimeter screw-capped test tubes into which 4.5 milliliter aliquots of the diluent prescribed in paragraph (a)(4) of this section have been dispensed. Two milliliters of thoroughly mixed vaccine are added to the first tube of the half-log series, mixed thoroughly, and 2.0 milliliters from this tube are transferred to the next tube in the series. The process of mixing and serially transferring 2.0 milliliters is repeated through each consecutive tube and 2.0 milliliters are discarded from the last tube.

(3) After the serial half-log dilutions are completed, 0.5 milliliter of 1.5 percent agar solution that has been cooled to 42° C is quickly added, where necessary, to make a final concentration of 0.15 percent agar, and the contents of the tubes are thoroughly mixed. After mixing, all tubes are incubated at 35° to 37° C for 3 to 4 weeks.

(4) The composition of modified Youman's medium with bovine albumin is as follows:

Asparagine	5.0 grams.
Monopotassium phosphate (KH_2PO_4).	Do.
Potassium sulfate (K_2SO_4)	0.5 grams.
Magnesium citrate	1.5 grams.
Monosodium glutamate	19.0 grams.
Glycerine	20.0 milliliters.
Distillled water q.s. to	900.0 milliliters.

One hundred milliliters of 5-percent aqueous solution of bovine albumin that has been sterilized by filtration are added to the Youman's medium to produce a final concentration of 0.5 percent of bovine albumin. The pH is adjusted to 7.0 with 5*N* sodium hydroxide.

(b) *Intradermal guinea pig test.* Two or more guinea pigs, each weighing no less than 250 grams, must be injected intradermally in 4 different sites with the following amounts and dilutions of each lot of BCG Vaccine:

(1) Vaccine intended for intradermal injection is reconstituted as for human use with the diluent recommended by the manufacturer. One-tenth milliliter of reconstituted vaccine and 0.1 milliliter each of three ten-fold dilutions (1:10, 1:100, and 1:1000) of the reconstituted vaccine are injected into the guinea pigs. The diluent for the ten-fold dilutions is isotonic solution for injection.

(2) Vaccine intended for percutaneous injection into humans is reconstituted with the diluent recommended by the manufacturer so that at least one human dose (estimated to be within a range of from 1 to 33×10^5 CFU) is contained in 0.1 milliliter. A narrower range of CFU is determined for each specific vaccine by the manufacturer and specified in the license application. One-tenth milliliter of the selected dose of vaccine and 0.1 milliliter each of three ten-fold dilutions (1:10, 1:100, and 1:1000) are injected into the guinea pigs. The diluent for the ten-fold dilutions is an isotonic solution for injection.

(3) The lot of vaccine is satisfactory if:

(i) At the end of 2 to 4 weeks after BCG vaccination, nodules have developed that are graded in relation to the amount of the test dose, with the largest dose inducing a nodule of from 4 to 10 millimeters in diameter and the smallest dose inducing essentially no nodule, and all observations are read on the same day;

(ii) By the end of 4 to 6 weeks after BCG vaccination, each guinea pig shows a degree of sensitivity such that an intradermal injection of no greater than 25 U.S. Tuberculin Units, Purified Protein Derivative, in 0.1 milliliter will induce an erythematous reaction at least 10 millimeters in diameter within 18 to 24 hours; and

(iii) At the end of the test period, each guinea pig is weighed and each shows a weight increase.

(c) *Induction of tuberculin sensitivity in tuberculin-negative humans.* At least once annually, no less than one lot of BCG Vaccine that has satisfied all requirements and has been released by the Center for Biologics Evaluation and Research must be tested for its ability to induce sensitivity in 20 persons negative to Tuberculin, Purified Protein Derivative, as prescribed in § 620.40(b)(4). The results of these tests must be sent to the Director, Center for Biologics Evaluation and Research, as they are completed.

[44 FR 14545, Mar. 13, 1979, as amended at 49 FR 23834, June 8, 1984; 55 FR 11013, Mar. 26, 1990]

§ 620.45 Test for freedom from virulent mycobacteria.

(a) Each lot of BCG Vaccine must be tested to determine that it does not contain virulent mycobacteria. The test must be performed using at least 6 guinea pigs, each weighing between 250 and 300 grams. Vaccine intended for intradermal injection in humans must be tested by injecting into guinea pigs the number of bacteria contained in at least 50 human doses. Vaccine intended for percutaneous use in humans must be tested by injecting into guinea pigs 50 times the number of bacteria estimated to be introduced parenterally into humans by the recommended procedure. The vaccine for all tests must be inoculated subcutaneously or intramuscularly into the guinea pigs. All animals that die during the observation period must be examined post-mortem. All animals that survive the observation period must be sacrificed and examined post mortem. The lot passes the test if at least two-thirds of the animals on test survive an observation period of not less than 6 weeks, and if the post-mortem examination reveals no evidence of tuberculosis in any of the test animals.

(b) If any virulent mycobacteria are found in any lot of BCG Vaccine, whether or not the manufacturer intends to submit samples and protocols of this lot to the Center for Biologics Evaluation and Research for release, the following actions must be taken:

(1) In addition to the requirements of §§ 600.12 and 600.14 of this chapter, the manufacturer shall immediately report by telephone, telegraph, or cable the finding of virulent mycobacteria to the Director, Center for Biologics Evaluation and Research.

(2) All production and distribution of lots of BCG Vaccine produced from the same secondary seed lot as the contaminated lot of BCG Vaccine must be discontinued. If no secondary seed lot is used the same requirements apply to the primary seed lot.

(3) The manufacturer shall conduct a thorough and prompt investigation concerning the failure of the lot to meet the required safety and purity specifications, including retesting the suspect lot and the source secondary seed lot (or primary seed lot, if no secondary seed lot is used) and shall undertake a thorough review of all manufacturing records and procedures to determine the probable cause of the failure.

(4) A written record of the investigation, including the retest results, must be submitted to the Director, Center for Biologics Evaluation and Research.

(5) Neither production nor distribution of BCG Vaccine may be resumed until the manufacturer is notified in writing by the Director, Center for Biologics Evaluation and Research, that such activity may be resumed.

[44 FR 14545, Mar. 13, 1979, as amended at 49 FR 23834, June 8, 1984; 55 FR 11013, Mar. 26, 1990]

§ 620.46 General requirements.

(a) *Dose.* These standards are based on (1) vaccine intended for intradermal injection in a single human immunizing dose of 0.1 milliliter and (2) vaccine intended for percutaneous injection in a single skin application through which inoculation is made by a multiple puncture device.

(b) *Date of manufacture.* The date of manufacture is the date of initiation of the last valid determination for CFU after freeze-drying.

§ 620.47 Labeling.

In addition to conforming to the applicable requirements of §§ 610.60, 610.61, and 610.62 of this chapter, the package label must bear the following information:

(a) Specification of the route of administration.

(b) A statement that the vaccine contains live bacteria and should be protected against exposure to light.

(c) A statement that the vaccine must be administered within 8 hours after reconstitution, and that reconstituted vaccine not used within 8 hours must be discarded.

§ 620.48 Samples; protocols; official release.

(a) For each lot of vaccine, the following materials must be submitted to the Director, Center for Biologics Evaluation and Research, Food and Drug Administration, 8800 Rockville Pike, Bethesda, MD 20892.

(1) Samples and diluent that will provide at least 20 milliliters when the samples are reconstituted as recommended in the package insert by the manufacturer of the vaccine.

(2) A protocol that consists of a complete summary of the manufacture of each lot, including all results of each test required by all applicable regulations. If the protocol is not included in the shipment of the samples, it must be sent promptly to the Director, Center for Biologics Evaluation and Research, Food and Drug Administration, 8800 Rockville Pike, Bethesda, MD 20892.

(b) The BCG Vaccine must not be issued by the manufacturer until written notification of official release is received from the Director, Center for Biologics Evaluation and Research, Food and Drug Administration.

[44 FR 14545, Mar. 13, 1979, as amended at 49 FR 23834, June 8, 1984; 51 FR 15610, Apr. 25, 1986; 55 FR 11013, Mar. 26, 1990]

PART 630—ADDITIONAL STANDARDS FOR VIRAL VACCINES

Subpart A—Poliovirus Vaccine Inactivated

Sec.

Subpart B—Poliovirus Vaccine Live Oral Trivalent

Subpart C—[Reserved]

Subpart D—Measles Virus Vaccine Live

Subpart E—[Reserved]

Subpart F—Mumps Virus Vaccine Live

Subpart G—Rubella Virus Vaccine Live

Subpart H—Smallpox Vaccine

AUTHORITY: Secs. 201, 501, 502, 503, 505, 510, 701 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, 351, 352, 353, 355, 360, 371); secs. 215, 351, 352, 353, 361 of the Public Health Service Act (42 U.S.C. 216, 262, 263, 263a, 264).

SOURCE: 38 FR 32068, 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—Poliovirus Vaccine Inactivated

§ 630.1 Poliovirus Vaccine Inactivated.

(a) *Proper name and definition.* The proper name of this product shall be ''Poliovirus Vaccine Inactivated'' which shall consist of an aqueous preparation of poliovirus types 1, 2, and 3, grown in monkey kidney tissue cultures, inactivated by a suitable method.

(b) *Strains of virus.* Strains of poliovirus used in the manufacture of vaccine shall be identified by historical records, infectivity tests and immunological methods. Any strain of virus may be used that produces a vaccine meeting the requirements of §§ 630.2, 630.3, and 630.4, but the Director, Center for Biologics Evaluation and Research may from time to time prohibit the use of any specific strain whenever he finds that it is practicable to use another strain of the same type that is potentially less pathogenic to man and that will produce a vaccine of at least equivalent safety and potency.

(c) *Monkeys; species permissible as source of kidney tissue.* Only Macaca or Cercopithecus monkeys, or a species found by the Director, Center for Biologics Evaluation and Research, to be equally suitable, which have met all requirements of §§ 600.11(f)(2) and 600.11(f)(8) of this chapter shall be used as a source of kidney tissue for the manufacture of Poliovirus Vaccine Inactivated.

[38 FR 32068, Nov. 20, 1973, as amended at 49 FR 23834, June 8, 1984; 50 FR 4137, Jan. 29, 1985; 55 FR 11013, Mar. 26, 1990]

§ 630.2 Poliovirus Vaccine Inactivated.

(a) *Cultivation of virus.* Virus for manufacturing vaccine shall be grown with aseptic techniques in monkey kidney cell cultures. Suitable antibiotics in the minimum concentration required may be used (§ 610.15(c) of this chapter).

(b) *Filtration.* Within 72 hours preceding the beginning of inactivation, the virus suspensions shall be filtered or clarified by a method having an efficiency equivalent to that of filtration through an S1 Seitz type filter pad.

(c) *Virus titer.* The 50 percent endpoint ($TCID_{50}$) of the virus fluids after filtration shall be $10^{6.5}$ or greater as confirmed by comparison in a simultaneous test (using groups of 10 tubes at 1 log steps or groups of 5 tubes at 0.5 log steps) with a reference virus distributed by the Center for Biologics Evaluation and Research. Acceptable titrations of the reference virus shall not vary more than ± 0.5 $\log_{10}$ from its labeled titer using 0.5 milliliter inoculum in tissue culture.

(d) *Inactivation of virus.* The virus shall be inactivated, as evidenced by the tests described in § 630.4, through the use of an agent or method which has been demonstrated to be consistently effective in the hands of the manufacturer in inactivating a series of lots of poliovirus. If formaldehyde is used for inactivation, it shall be added to the virus suspension to a final concentration of U.S.P. solution of formaldehyde of 1:4000, and the inactivation conducted under controlled conditions of pH and time, at a temperature of 36° to 38° C. Three or more virus titers, suitably spaced to indicate rate of inactivation, shall be determined during the inactivation process. Filtration equivalent to that described in paragraph (b) of this section shall be performed after the estimated baseline time (time at which the 50 percent end-

point reaches one tissue culture infective dose per milliliter), but prior to sampling for the first single strain tissue culture test required in §630.4(b), except that this filtration may be omitted for strains of a virulence for monkeys equal to or less than that of the MEF–1 Type 2 strain of poliovirus.

(e) *Additional processing.* Single strain or trivalent pools that have failed to pass safety tests prescribed in §630.4 (b), (c), or (e) may be treated as follows:

(1) Filtration or clarification by a method having an efficiency equivalent to that of filtration through an S1 Seitz type filter pad.

(2) Negative tests performed as described in §630.4 (b) and (c) must be obtained on each of two successive samples taken so as to be separated by an interval of at least 3 days while the material is being subjected to treatment with 1:4000 U.S.P. formaldehyde solution and heat at 36° to 38° C. The first sample may be taken before incubation is begun and the second sample shall be taken after the incubation of at least 3 days is completed. For both single strain and trivalent pools the volume tested for each tissue culture safety test shall be equivalent to at least 1,500 human doses.

(3) Pools which are positive following such additional processing shall not be used for the manufacture of Poliovirus Vaccine Inactivated

(f) *Supplemental inactivation.* Supplemental inactivation employing a method capable of reducing the titer of a similarly produced virus suspension by a factor of 10^{-6} may be applied at any point after the filtration step described in paragraph (d) or (e)(1) of this section.

[38 FR 32068, Nov. 20, 1973, as amended at 49 FR 23834, June 8, 1984; 50 FR 4137, Jan. 29, 1985; 55 FR 11013, Mar. 26, 1990]

§630.3 Potency test.

Each lot of vaccine shall be subjected to a potency test which permits an estimation of the antigenic capacity of the vaccine. This is done by means of a simultaneous comparison of the serum antibody levels produced in monkeys by the vaccine under test with the antibody level of the reference serum distributed by the Center for Biologics Evaluation and Research. The potency test shall be performed on samples taken after all final processing of the product has been completed, including addition of preservative, except that when the final product contains material having an adjuvant effect an additional test shall be performed with a sample taken before the addition of the adjuvant material. The volume of the test sample for the additional test shall be adjusted to the equivalent volume of Poliovirus Vaccine Inactivated in the final product. The test shall be conducted as follows:

(a) *Inoculation of monkeys.* A group of 12 or more Macaca monkeys, or a species found by the Director, Center for Biologics Evaluation and Research, to be equally suitable for the purpose, shall be used. Animals shall weigh between 4 and 8 pounds and shall be in overt good health. Animals that become ill and remain ill during the course of immunization shall be excluded from the group. The test shall not be valid unless at least 10 animals survive the test period and their preinoculation serum antibody levels are as prescribed in paragraph (d) of this section. The test vaccine shall be given intramuscularly to each monkey in 3 doses at 7-day intervals, each dose to be the recommended individual human dose. Only undiluted vaccine shall be used.

(b) *Serum samples.* A blood sample shall be taken from each monkey prior to vaccination and then again 7 days after the last injection. Serum shall be separated aseptically, and stored under refrigeration.

(c) *Serum-virus neutralization test.* The titers of individual monkey serums shall be determined in comparison with the reference serum in tests designed to include controls for all the variables of significance including the following:

(1) Serum toxicity control;

(2) Cell control and cell titration;

(3) Virus titration control (at least 4 tubes for each dilution at 0.5 log steps); and

(4) Serum controls using type-specific serums to identify the type of virus used in the neutralization test.

(d) *Interpretation of the test.* Animals showing preinoculation titers of 1:4 or over when tested against not more

than 1,000 $TCID_{50}$ of virus, shall be excluded from the test. The geometric mean titer of antibody induced in the monkeys surviving the course of immunization and bleeding, shall be calculated. A comparison of the value so obtained shall be made with the value for the reference serum that was tested simultaneously and expressed as the ratio between the geometric mean titer value of the serums under test and the mean titer value of the reference serum.

(e) *Potency requirements.* A lot of vaccine tested against the reference serum shall be satisfactory if the geometric mean value of the group of individual monkey serums representing the lot of vaccine tested is at least 1.29 times the mean value of the reference serum for Type 1, at least 1.13 times for Type 2, and at least 0.72 times for Type 3.

[38 FR 32068, Nov. 20, 1973, as amended at 49 FR 23834, June 8, 1984; 50 FR 4137, Jan. 29, 1985; 55 FR 11013, Mar. 26, 1990]

§ 630.4 Tests for safety.

In the manufacture of the product, the following tests relating to safety shall be conducted by the manufacturer.

(a) *The virus pool—tests prior to inactivation*—(1) *B virus and Mycobacterium tuberculosis.* Prior to inactivation, each individual virus harvest or virus pool shall be tested for the presence of B virus and Mycobacterium tuberculosis.

(2) *SV–40.* Prior to inactivation, the material shall be tested for the presence of SV–40 as follows (or by any other test producing equally reliable results): A sample of at least 5 ml. from the virus harvest or virus pool shall be neutralized by high titer specific antiserum of other than primate origin. A similar sample from the pool of tissue culture fluids from control vessels representing the tissue from which the virus was prepared may be tested in place of the virus sample. The sample shall be tested in primary cercopithecus tissue cultures or in a cell line demonstrated as at least equally susceptible to SV–40. Each tissue culture system shall be observed for at least 14 days and at the end of the observation period at least one subculture of fluid shall be made in the same tissue culture system and the subculture shall be observed for at least 14 days.

(3) *Test results.* The virus harvest or virus pool is satisfactory for poliovirus vaccine only if the tests produce no evidence of the presence of B virus, Mycobacterium tuberculosis or SV–40.

(b) *Single strain pool tissue culture tests for poliovirus.* (1) Before pooling to make the final poliovirus vaccine, during inactivation at 36° to 38° C., two samples of each monovalent bulk strain pool shall be tested for the presence of virus by tissue culture methods, the second sample to be taken at least 3 days after taking the first sample.

(2) Each sample shall be no smaller than the equivalent of 1,500 human doses and shall be subjected to the complete testing process and each test shall be performed on a different monkey kidney tissue culture cell preparation. The test sample for one of these tests may be used also for the test prescribed in paragraph (f) of this section provided the cell cultures used have been demonstrated as fully susceptible to SV–40 and poliovirus. Each sample shall be inoculated into five or more tissue culture bottles of a suitable capacity, the ratio of the vaccine to the nutrient fluid being approximately 1:1 to 1:3, and the area of the surface growth of cells being at least 3 square centimeters per milliliter of sample. The tissue culture bottles shall be observed for at least 14 days.

(3) A first subculture shall be made at the end of 7 days from date of inoculation by planting at least 2 percent of the volume from each original bottle into suitable tissue culture vessels, followed by refeeding.

(4) A second subculture shall be made from each original bottle in the same manner at the end of 14 days from date of inoculation.

(5) Each of the first and second subcultures shall be observed for at least 7 days.

(6) If cytopathogenic effects occur either in the original bottles of the two tests or in the subcultures from them, or if cellular degeneration appears in the original bottles or in the subcultures before degeneration occurs in uninoculated cultures, the pool shall be

held until the matter is resolved. If active poliovirus is indicated, the strain pool shall not be used for inclusion in a final vaccine unless effectively reprocessed as described in §630.2(e). If other viruses are present, the pool shall not be used unless it can be demonstrated that such viruses have originated from other than the strain pool being tested.

(c) *Trivalent vaccine pool tissue culture test.* No less than 1,500 human doses of the trivalent vaccine pool, without final preservative, prepared by pooling the three type pools, each of which has passed all tests prescribed in paragraph (b) of this section, shall be subjected to the complete tissue culture test prescribed in such paragraph (b) in at least two approximately equal tests in separate monkey kidney tissue culture preparations. This test sample may be used also for the test prescribed in paragraph (f) of this section provided the cell cultures used have been demonstrated as fully susceptible to SV–40 and poliovirus.

(d) *Trivalent vaccine pool lymphocytic choriomeningitis test.* The final vaccine shall be shown to be free of lymphocytic choriomeningitis virus by intracerebral inoculation of the maximum volume tolerated into 10 or more mice which shall be observed daily for at least 21 days and a negative test shall not be valid unless at least eight mice survive for this period.

(e) *Test in monkeys for active virus.* (1) Vaccine from final containers selected at random from each filling of each lot shall be pooled to provide a test sample of at least 400 milliliters representing the various fillings. An equal volume of bulk vaccine may be substituted for test samples from each filling lot provided the procedure has been approved by the Director, Center for Biologics Evaluation and Research.

(2) A total of not less than 20 monkeys shall be inoculated with the test sample. A preinjection serum sample from each monkey must not contain neutralizing antibody against the three poliovirus types detectable in a dilution of 1:4 when tested against not more than 1,000 $TCID_{50}$ of virus. At least 80 percent of the test animals representing each filling or each bulk sample must survive the test period without significant weight loss, except that if at least 60 percent of the test animals survive the first 48 hours after injection, those animals which do not survive this 48-hour test period may be replaced by an equal number of test animals. At least 80 percent of the animals used in the test must show microscopic evidence of inoculation trauma in the lumbar region of the spinal cord, and gross or microscopic evidence of inoculation trauma in the thalamic area. If less than 60 percent of the test animals survive the first 48 hours, or if less than 80 percent of the animals fail to meet the other criteria prescribed in this section, the test must be repeated.

(3) Vaccines shall be injected by combined intracerebral, intraspinal, and intramuscular routes into Macaca or Cercopithecus monkeys or a species found by the Director, Center for Biologics Evaluation and Research, to be equally suitable for the purpose. The animals shall be in overt good health and injected under deep barbiturate anesthesia. The intracerebral injection shall consist of 0.5 milliliter of test sample into the thalamic region of each hemisphere. The intraspinal injection shall consist of 0.5 milliliter of concentrated test sample into the lumbar spinal cord enlargement, the test sample to be concentrated 100 fold in the ultracentrifuge by a method demonstrated to recover at least 90 percent of the virus particles in the sediment after it has been resuspended in the same lot of unconcentrated test sample. The intramuscular injection shall consist of 1.0 milliliter of test sample into the right leg muscles. At the same time, 200 milligrams of cortisone acetate shall be injected into the left leg muscles, and 1.0 milliliter of procaine penicillin (300,000 units) into the right arm muscles. The monkeys shall be observed for 17 to 19 days and signs suggestive of poliomyelitis shall be recorded.

(4) At the end of the observation period, samples of cerebral cortex and of cervical and lumbar spinal cord enlargements shall be taken for virus recovery and identification. Histological sections shall be prepared from both spinal cord enlargements and examined.

(5) Doubtful histopathological findings necessitate (i) examination of a sample of sections from several regions of the brain in question, and (ii) attempts at virus recovery from the nervous tissues previously removed from the animal. The test results must be negative. Test results are negative if the histological and other studies leave no doubt that poliovirus infection did not occur.

(f) *Tissue culture safety test for SV–40.* At least 500 human doses of each monovalent or trivalent pool of vaccine shall be tested for the presence of SV–40 using primary cercopithecus monkey tissue cultures or using a cell line demonstrated as at least equally susceptible to SV–40. The test shall be conducted as described in paragraph (b) of this section, except for the volume of test sample and except that one subculture of at least 2 percent of the volume of the fluids shall be made no less than 14 days from the date of inoculation and examined for at least 14 days from the date of subinoculation. The vaccine is satisfactory only if there is no evidence of the presence of SV–40 in any of the cultures or subcultures.

[38 FR 32068, Nov. 20, 1973, as amended at 49 FR 23834, June 8, 1984; 50 FR 4137, Jan. 29, 1985; 50 FR 16229, Apr. 25, 1985; 55 FR 11013, Mar. 26, 1990; 57 FR 10814, Mar. 31, 1992]

§ 630.5 General requirements.

(a) *Consistency of manufacture.* No lot of final vaccine shall be released unless it is one of a series of five consecutive lots produced by the same manufacturing process, all of which have shown negative results with respect to all tests for the presence of live poliovirus, and unless each of the monovalent pools of which a polyvalent final vaccine is composed similarly is one of a series of five consecutive monovalent pools of the same type of inactivated poliovirus, all of which have shown negative results in all tests for the presence of live poliovirus.

(b) *Dose.* These additional standards are based on a human dose of 1.0 milliliter for a single injection and a total human immunizing dose of three injections of 1.0 milliliter given at appropriate intervals.

(c) *Samples and protocols.* For each lot of vaccine, the following material shall be submitted to the Director, Center for Biologics Evaluation and Research, Food and Drug Administration, 8800 Rockville Pike, Bethesda, MD 20892:

(1) A 2,500 milliliter sample, neutralized, not dialyzed, and without final preservative, taken at the latest possible stage of manufacturing before the addition of such preservative.

(2) A 200 milliliter bulk sample of the final vaccine containing final preservative.

(3) A total of not less than a 200 milliliter sample of the final vaccine in final labeled containers.

(4) A protocol which consists of a summary of the history of manufacture of each lot including all results of each test for which test results are requested by the Director, Center for Biologics Evaluation and Research.

[38 FR 32068, Nov. 20, 1973, as amended at 49 FR 23834, June 8, 1984; 51 FR 18580, May 21, 1986; 55 FR 11013, Mar. 26, 1990]

Subpart B—Poliovirus Vaccine Live Oral Trivalent

SOURCE: 56 FR 21432, May 8, 1991, unless otherwise noted.

§ 630.10 Poliovirus Vaccine Live Oral Trivalent.

(a) *Proper name and definition.* The proper name of this product shall be Poliovirus Vaccine Live Oral Trivalent. The vaccine shall be a preparation containing the three types of live, attenuated polioviruses grown in monkey kidney cell cultures, or in a cell line found by the Director, Center for Biologics Evaluation and Research, to meet the requirements of §610.18(c) of this chapter. The vaccine shall be prepared in a form suitable for oral administration.

(b) *Criteria for acceptable strains.* (1) The Sabin strains of attenuated poliovirus, Type 1 (LS-c, 2ab/KP_2), Type 2 (P712, Ch, 2ab/KP_2), and Type 3 (Leon $12a_1b/KP_3$), or derivatives from them, may be used in the manufacture of vaccine.

(2)(i) Other poliovirus strains may be used in the manufacture of Poliovirus Vaccine Live Oral Trivalent provided that they are identified by historical records including:

(A) Origin,

(B) Techniques of attenuation,

(C) Antigenic properties,

(D) Neurovirulence for monkeys,

(E) Pathogenicity for tissue cultures of various cell types, and

(F) Established virus markers, including rct/40, and d.

(ii) The data shall be submitted to the Director, Center for Biologics Evaluation and Research, along with other data that establish:

(A) That each such strain is at least as safe as the Sabin strain of the corresponding type,

(B) That each such strain demonstrates results comparable to the Sabin srain when inoculated into monkeys by the intrathalamic and intramuscular routes, and

(C) That each such strain has been used to produce vaccines meeting the safety and potency requirements of §§ 630.11, 630.15, 630.16 or 630.17, and 630.18.

(3) The Director, Center for Biologics Evaluation and Research, may prohibit the use of a specified strain whenever the Director finds that it is practicable to use another strain of the same type that will produce a vaccine of greater safety and of at least equivalent potency.

(4) If vaccine lots have been produced directly from strain materials (e.g., Sabin Original, Sabin Original Merck, or Sabin Original Rederived), the strain material is not required to be tested in accordance with the provisions of § 630.10(c).

(c) *Criteria for qualification of the seed virus.* (1) Each seed virus used in vaccine manufacture shall be prepared from an acceptable strain in monkey kidney cell cultures, derived from animals which have met all of the requirements of § 630.12(a), or in a cell culture of a type determined to be suitable by the Director, Center for Biologics Evaluation and Research. The seed virus used in vaccine manufactures shall be demonstrated to be free of extraneous microbial agents except for unavoidable bacteriophage.

(2) Seed virus used for the manufacture of oral poliovirus vaccine shall meet the requirements of §§ 630.13, 630.16 or 630.17, and 630.18. In addition, the neurovirulence of each of the first five consecutive monovalent virus pools prepared from the seed virus shall meet the neurovirulence requirements prescribed in §§ 630.16(b)(2) or 630.17 (b)(3).

(3) A new seed virus may be used for production provided data are submitted in the form of a product license a supplement that show the new seed virus and each of the first five consecutive monovalent virus pools prepared from it meet the safety requirements of §§ 630.13 and 630.16 or 630.17 and 630.18 and approval for the use of the seed virus is received in writing from the Director, Center for Biologics Evaluation and Research.

(4) Seed virus in vaccine manufacture shall be prepared in a seed lot system from a master virus seed lot at a passage level consistent with § 630.13(a).

(5) For monovalent virus pools tested in accordance with § 630.16(b), the use of the seed virus may continue provided that the frequency of monovalent virus pools produced with it which fail to meet the criteria of neurovirulence for monkeys prescribed in § 630.16(b)(2) is not greater than predicted on the basis of comparison with the corresponding reference preparation. If the frequency of monovalent virus pools produced with the same seed virus which fail to meet the criteria of neurovirulence for monkeys prescribed in §§ 630.16(b)(2) is greater than the predicted 1 percent on the basis of the 99-percent fiduciary one-sided upper limit, that seed virus shall be disqualified for further use in vaccine production.

(6) For monovalent virus pools tested in accordance with § 630.17, subsequent and identical neurovirulence tests of the seed virus shall be performed in monkeys whenever there is evidence of a significant increase in the neurovirulence of the seed virus, upon introduction of a new production seed lot, and as often as is necessary to otherwise establish, to the satisfaction of the Director, Center for Biologics Evaluation and Research, that the seed virus for vaccine manufacture has maintained its neurovirulence properties as set forth in § 630.17 (b)(3).

[56 FR 21432, May 8, 1991, as amended at 59 FR 49351, Sept. 28, 1994]

§ 630.11 Clinical trials to qualify for license.

To qualify for license, the antigenicity of the vaccine shall have been determined by clinical trials of adequate statistical design conducted in compliance with part 56 of this chapter, unless exempted under § 56.104 or granted a waiver under § 56.105, and with part 50 of this chapter. Such clinical trials shall be conducted with five lots of oral poliovirus vaccine that have been manufactured by the same methods. Type specific neutralizing antibody for each type of poliovirus in the vaccine shall be induced in 90 percent or more of susceptibles after a series of doses.

§ 630.12 Animal source and quarantine; personnel.

(a) *Monkeys*—(1) *Species permissible as source of kidney tissue.* Only Macaca monkeys, Cercopithecus monkeys, or other species found by the Director, Center for Biologics Evaluation and Research, to be equally suitable, which meet the requirements of § 600.11 (f)(2) and (f)(8) of this chapter, shall be used as the source of kidney tissue for the manufacture of Poliovirus Vaccine Live Oral Trivalent.

(2) *Experimental and test monkeys.* Monkeys that have been used previously for experimental or test purposes shall not be used as a source of kidney tissue in the processing of vaccine.

(3) *Quarantine; additional requirements.* Excluding deaths from accidents or causes not due to infectious diseases, if the death rate of any group of monkeys being conditioned in accordance with § 600.11(f)(2) of this chapter exceeds 5 percent per month, the remaining monkeys may be used for the manufacture of Poliovirus Vaccine Live Oral Trivalent only if all of the monkeys survive a new quarantine period.

(b) *Personnel.* All reasonably possible steps shall be taken to ensure that personnel involved in processing the vaccine are immune to all three types of poliovirus and do not excrete poliovirus.

[56 FR 21432, May 8, 1991; 56 FR 27787, June 17, 1991]

§ 630.13 Manufacture of Poliovirus Vaccine Live Oral Trivalent.

(a) *Virus passages.* Virus in the final vaccine shall represent no more than five tissue culture passages from the original strain or no more than five tissue culture passages from a virus clone derived from one of the first five tissue culture passages of the original strain.

(b) *Virus propagated in primary monkey kidney cell cultures*—(1) *Continuous cell lines.* When primary monkeys kidney cell cultures are used in the manufacture of poliovirus vaccine, continuous cell lines shall not be introduced or propagated in vaccine manufacturing areas.

(2) *Identification of processed kidneys.* The kidneys from each monkey shall be processed separately. The resulting viral fluid shall be identified as a separate monovalent harvest and kept separately from other monovalent harvests until all samples for the tests prescribed in paragraphs (b)(3) and (b)(4) of this section relating to that pair of kidneys have been withdrawn from the harvest.

(3) *Monkey kidney tissue production vessels prior to virus inoculation.* Prior to inoculation with the seed virus and at least 3 days after complete formation of the tissue sheet, the tissue culture growth in vessels derived from each pair of kidneys shall be examined microscopically for evidence of cell degeneration. If such evidence is observed, the tissue cultures from that pair of kidneys shall not be used for poliovirus vaccine manufacture. To test the tissue found free of cell degeneration for further evidence of freedom from demonstrable viable microbial agents, the fluid shall be removed from the cell cultures immediately prior to virus inoculation and tested in each of four culture systems:

(i) Macaca monkey kidney cells,

(ii) Cercopithecus monkey kidney cells,

(iii) Primary rabbit kidney cells, and

(iv) Cells from one of the systems described in § 630.18(a)(6).

The fluid shall be tested in the following manner: Aliquots of fluid from each vessel derived from the same pair of kidneys shall be pooled and at least 10 milliliters of the pool inoculated into each system. The dilution of the

pool with medium shall be no greater than 1:4 and the area of surface growth of cells shall be at least 3 square centimeters per milliliter of test inoculum. The cultures shall be observed for at least 14 days. At the end of the observation period, at least one subculture of fluid from the Cercopithecus monkey kidney cell cultures shall be made in the same tissue culture system and the subculture shall be observed for at least 14 days. If these tests indicate the presence in the monkey kidney tissue culture production vessels of any viable microbial agent, the viral harvest from these tissue cultures so implicated shall not be used for poliovirus vaccine manufacture.

(4) *Control vessels.* At least 25 percent of the cell suspension from each pair of kidneys shall be set aside and used to establish control cultures. The control cultures shall be examined microscopically for cell degeneration for an additional 14 days. The culture fluids from such control cells shall be tested, both at the time of virus harvest and at the end of the additional observation period, by the method prescribed for testing of fluids in paragraph (b)(3) of this section. In addition, the control cell sheet shall be examined for presence of hemadsorbing viruses by the addition of guinea pig red blood cells.

(5) *Interpretation of test results.* At least 80 percent of the control vessels shall be free of cell degeneration at the end of the observation period to qualify the kidneys for poliovirus vaccine manufacture. If the test results of the control cells indicate the presence of any extraneous agent at the time of virus harvest, the virus harvest from that tissue culture preparation shall not be used for poliovirus vaccine manufacture. If any of the tests or observations described in paragraph (b)(3) or (b)(4) of this section demonstrate the presence in the tissue culture preparation of any microbial agent known to be capable of producing human disease, the virus grown in each tissue culture preparation shall not be used for poliovirus vaccine manufacture.

(6) *Temperature of kidney tissue production vessels after virus inoculation.* After virus inoculation, production vessels shall be maintained at 33.0 to 35.0 °C during the course of virus propagation.

(7) *Kidney tissue virus harvests.* Virus shall be harvested not later than 72 hours after virus inoculation. Virus harvested from vessels containing the kidney tissue from one monkey may be tested separately, or samples of viral harvests from more than one pair of kidneys may be combined, identified, and tested as a monovalent virus pool. Each pool shall be mixed thoroughly and samples withdrawn for testing as prescribed in §630.18(a). The samples shall be withdrawn immediately after harvesting and prior to further processing, except that samples of test materials frozen immediately after harvesting and maintained at −60 °C or below, may be tested upon thawing, provided no more than one freeze-thaw cycle is employed.

(8) *Filtration.* After harvesting and removal of samples for the safety tests prescribed in §630.18(a), the pool shall be passed through sterile filters having a sufficiently small porosity to assure bacteriologically sterile filtrates.

[56 FR 21432, May 8, 1991, as amended at 58 FR 19609, Apr. 15, 1993]

§630.14 Reference virus preparations.

(a) *Titration test controls.* The following reference viruses may be obtained from the Center for Biologics Evaluation and Research:

(1) Reference Poliovirus, Live, Attenuated, Type 1, as a control for correlation of virus titers in tissue cultures.

(2) Reference Poliovirus, Live, Attenuated, Type 2, as a control for correlation of virus titers in tissue cultures.

(3) Reference Poliovirus, Live, Attenuated, Type 3, as a control for correlation of virus titers in tissue cultures.

(4) Reference Poliovirus, Live, Attenuated, Trivalent, as a control for correlation of virus titers in tissue cultures.

(b) *Neurovirulence test controls.* (1) Except as provided in paragraph (b)(2) of this section, the following reference virus may be obtained from the Center for Biologics Evaluation and Research:

(i) Reference Attenuated Poliovirus, Type 1, as a control for evaluation of monkey neurovirulence tests.

(ii) Reference Attenuated Poliovirus, Type 2, as a control for evaluation of monkey neurovirulence tests.

(iii) Reference Attenuated Poliovirus, Type 3, as a control for evaluation of monkey neurovirulence tests.

(2) Alternatively, upon FDA approval, World Health Organization (WHO) reference standards of the corresponding type, WHO/I, WHO/II, and WHO/III, may be used as controls for evaluation of monkey neurovirulence tests.

§ 630.15 Potency test.

(a) *Test for virus titer.* The concentration of living virus in each monovalent virus pool and in each trivalent vaccine, expressed as infectivity titer per milliliter for cell cultures, shall be determined using the Reference Poliovirus, Live, Attenuated of the same type as a control or using another reference preparation of the same type that has been calibrated against the appropriate reference preparation listed in §630.14(a). A titration of the monovalent virus pool or the trivalent vaccine shall not constitute a valid test unless the titration of the reference virus when tested in parallel is within ± 0.5 $\log_{10}$ of its established titer. The titration of the parallel reference is intended to validate the test system and shall not be used to adjust the titer of the pool or lot under test.

(b) *Dose.* The human dose of trivalent vaccines shall be constituted to have infectivity titers in the final container material of $10^{6.0}$ to $10^{7.0}$ for type 1, $10^{5.1}$ to $10^{6.1}$ for type 2, and $10^{5.8}$ to $10^{6.8}$ for type 3, when assayed in HEp–2 cells, or the equivalent when titrated by a different method.

§ 630.16 Test for neurovirulence.

(a) Except as provided in §630.17, the following test relating to safety prescribed in paragraph (b) of this section shall be performed on each monovalent virus pool after the filtration process.

(b) *Neurovirulence in monkeys.* Except as provided in paragraph (b)(5) of this section, each monovalent virus pool shall be tested concurrently with the corresponding type Reference Attenuated Poliovirus for neurovirulence by the intraspinal route of injection in Macaca monkeys. Whenever possible the monkeys should be of comparable age and weight and from the same quarantine group. The monkeys shall be distributed randomly between the two test groups. If the number of monkeys included in both groups precludes completion during a single workday, approximately equal numbers of monkeys shall be inoculated with the monovalent virus pool and the reference preparation during each of the testing days. A preinjection serum sample obtained from each monkey shall be shown to contain no neutralizing antibody in a dilution of 1:4 when tested against no more than 1,000 $TCID_{50}$ (mean tissue culture infectious doses) of each of the three types of poliovirus. The neurovirulence test is not valid unless the inoculation sample is shown to contain the equivalent of $10^{6.5}$ to $10^{7.5}$ $TCID_{50}$ per milliliter when a representative sample of the monovalent virus pool is titrated in HEp-2 cells in comparison with the Reference Poliovirus, Live, Attenuated of the appropriate type. All monkeys shall be observed for 17 to 21 days and any evidence of physical abnormalities indicative of poliomyelitis or other viral infections shall be recorded.

(1) *Intraspinal inoculation.* For tests with type 1 and type 2 monovalent virus pools and the Reference Attenuated Poliovirus of the corresponding types, each of a group of at least 12 monkeys after being suitably anesthetized shall be injected intraspinally into the enlargement of the lumbar cord with 0.1 milliliter of the inoculation sample. For tests with type 3 poliovirus materials, groups of at least 20 monkeys shall be injected as above after being suitably anesthetized. A test of a virus pool shall include at least one group of monkeys, and no more than three groups shall be inoculated, with the results from testing one, two, or three groups of monkeys being evaluated as prescribed in §630.16(b)(2). In addition, if on examination there is no evidence of correct inoculation, additional animals may be inoculated in order to reestablish the minimum number of 11 positive monkeys for tests of types 1 and 2 virus

pools and the minimum number of 18 positive monkeys for tests of Type 3 virus pools. A positive monkey is an animal which either survives for 11 or more days or succumbs or is sacrificed due to a severe poliovirus infection at any time before the 11th day of the observation period and in which neural lesions specific for poliovirus are seen in the central nervous system. If at least 60 percent of the animals of a group survive 48 hours after inoculation, those animals that did not survive may be replaced by additional animals. If less than 60 percent of the animals in a group survive 48 hours after inoculation, the test shall be considered invalid and shall be repeated.

(2) *Determination of neurovirulence.* At the conclusion of the observation period, the animals are sacrificed and a comparative evaluation shall be made of the evidence of neurovirulence of the monovalent virus pool under test and the Reference Attenuated Poliovirus of the corresponding type with respect to the histopathology of lesions caused by poliovirus. Animals dying or sacrificed when severely paralyzed or moribund during the test period, should be included in the evaluation, except that these examinations of these monkeys shall be made immediately after death. Histopathological examinations by a qualified pathologist shall be made of at least the lumbar and cervical enlargements, the medulla, the mesencephalon, the thalamus, and motor cortex of each monkey in the groups injected with the monovalent virus pool or with the reference under test. The magnitude of the neuropathology exhibited in the lumbar and cervical areas, the medulla, and mesencephalon of all positive monkeys inoculated with the monovalent virus pool shall be quantified and compared to the magnitude of the neuropathology determined based on the same type of evaluation of monkeys in the current test and all previous tests of the Reference Attenuated Poliovirus of the corresponding type. The monovalent virus pool may be used for poliovirus vaccine if a comparative analysis of the test results demonstrates that the numerical value assigned for neurovirulence of the monovalent virus pool is equal to or less than that of the Reference Attenuated Poliovirus of the corresponding type. If the numerical value assigned for neurovirulence of the monovalent virus pool is greater than that of the Reference Atteneuated Poliovirus, the monovalent virus pool is acceptable if the difference is not greater than that calculated by a mathematical method that is expected to reject vaccines with neurovirulence identical to the reference at a frequency of not less than 1 in 100 when 1 group of monkeys is inoculated. If 2 groups are injected with the same monovalent virus pool under test, the frequency of rejection shall be not less than 5 in 100 and for 3 groups, not less than 10 in 100. If the difference in numerical values is greater than that calculated, irrespective of which reference preparation was used in the test, the monovalent virus pool shall be considered unacceptable and shall not be used for vaccine manufacture.

(3) *Outlier scores.* In the event that one or more monkeys inoculated with virus from the monovalent virus pool have individual mean lesion scores higher than that previously or concurrently associated with the Reference Attenuated Poliovirus of the corresponding type, but the monovalent virus pool meets the criteria for acceptable neurovirulence given in §630.16(b)(2), the significance of the outlier scores shall be evaluated by a method approved by the Director, Center for Biologics Evaluation and Research before the vaccine may be released for use.

(4) *Test with Reference Attenuated Poliovirus.* Except as provided in paragraph (b)(5) of this section, the Reference Attenuated Poliovirus of the appropriate type shall be tested as prescribed in paragraph (b)(1)(i) of this section concurrently with the monovalent virus pool. More than one monovalent virus pool of the same type may be tested with the same corresponding Reference Attenuated Poliovirus. Initially, a minimum of four tests by the testing laboratory of each Reference Attenuated Poliovirus is required. These tests must be such as to provide sufficient experience to define the performance of the Reference Attenuated Poliovirus and establish the variability of the assay. Each test of

the Reference Attenuated Poliovirus shall be considered acceptable and added to the previous testing experience only if the magnitude of its poliovirus neuropathology is statistically compatible with the results of all previous tests with the same reference preparations of the same type performed by the testing laboratory.

(5) *Alternative procedures in case of monkey shortage.* In the event of a shortage of test monkeys and upon approval of the Director, Center for Biologics Evaluation and Research, a monovalent virus pool may be tested without concurrent testing of the corresponding type Reference Attenuated Poliovirus. In such a case, the magnitude of the neuropathology of the monovalent virus pool shall be compared with the magnitude of the neuropathology exhibited in all previous tests of the corresponding Reference Attenuated Poliovirus.

§ 630.17 Alternative test for neurovirulence.

(a) In lieu of the neurovirulence test in § 630.16, the following test may be performed after the filtration process, on each monovalent virus pool or on each multiple thereof (monovalent lot).

(b) *Neurovirulence in monkeys.* Each monovalent virus pool or monovalent lot shall be tested in comparison with the Reference Attenuated Poliovirus, Type 1, for neurovirulence in Macaca monkeys by both the intrathalamic and intraspinal routes of injection. A preinjection serum sample obtained from each monkey must be shown to contain no neutralizing antibody in a dilution of 1:4 when tested against no more than 1,000 $TCID_{50}$ (mean tissue culture infectious dose) of each of the three types of poliovirus. The neurovirulence tests are not valid unless the sample contains at least $10^{7.6}$ $TCID_{50}$ per milliliter when titrated in HEp-2 cells in comparison with the Reference Poliovirus, Live, Attenuated of the appropriate type. All monkeys shall be observed for 17 to 21 days and any evidence of physical abnormalities indicative of poliomyelitis or other viral infections shall be recorded.

(1) *Intrathalamic inoculation.* Each of at least 30 monkeys shall be injected intracerebrally by placing 0.5 milliliter of virus pool material into the thalamic region of each hemisphere. Comparative evaluations shall be made with the virus pool under test and the Reference Attenuated Poliovirus, Type 1. Only monkeys that show evidence of inoculation into the thalamus shall be considered as having been injected satisfactorily. With respect to inoculation, a test is deemed valid if at least 24 monkeys are considered as having been injected satisfactorily. If on examination there is evidence of failure to inoculate virus pool material into the thalamus, additional monkeys may be inoculated in order to reestablish the minimum number of monkeys for the test.

(2) *Intraspinal inoculation.* Each of a group of at least five monkeys shall be injected intraspinally with 0.2 milliliter of virus pool material containing at least $10^{7.6}$ $TCID_{50}$ per milliliter when titrated in HEp-2 cells, and each monkey in additional groups of at least five monkeys shall be injected intraspinally with 0.2 milliliter of a 1:1,000 and 1:10,000 dilution, respectively, of the same virus pool material. Comparative evaluations shall be made with the virus pool under test and the reference material. Only monkeys that show microscopic evidence of inoculation into the gray matter of the lumbar cord shall be considered as having been injected satisfactorily. With respect to inoculation, a test is deemed valid if at least four monkeys per group are considered as having been injected satisfactorily. If on examination there is evidence of failure to inoculate intraspinally, additional animals may be inoculated in order to reestablish the minimum number of animals per group.

(3) *Determination of neurovirulence.* At the conclusion of the observation period comparative histopathological examinations by a qualified pathologist shall be made of the lumbar cord, cervical cord, lower medulla, upper medulla, mesencephalon and motor cortex of each monkey in the groups injected with virus under test and those injected with the Reference Attenuated Poliovirus, Type 1, except that for animals dying during the test period, these examinations shall be made immediately after death. If at least 60

percent of the animals of a group survive 48 hours after inoculation, those animals which did not survive may be replaced by an equal number of animals tested as prescribed in paragraph (b) of this section. If less than 60 percent of the animals of a group survive 48 hours after inoculation, the test must be repeated. At the conclusion of the observation the animals shall be examined to ascertain whether the distribution and histological nature of the lesions are characteristics of poliovirus infection. A comparative evaluation shall be made of the evidence of neurovirulence of the virus under test and the Reference Attenuated Poliovirus, Type 1, with respect to:

(i) The number of animals showing lesions characteristic of poliovirus infection;

(ii) The number of animals showing lesions other than those characteristic of poliovirus infection;

(iii) The severity of the lesions;

(iv) The degree of dissemination of the lesions; and

(v) The rate of occurrence of paralysis not attributable to the mechanical injury resulting from inoculation trauma. These five factors may be weighted and interpreted as the Director, Center for Biologics Evaluation and Research, or the Director's delegatees deem appropriate. Among permissible interpretations, the factors may be considered in different ways for monkeys inoculated intraspinally and for monkeys inoculated intrathalamically. Other relevant factors in addition to those listed in paragraph (b)(3)(i) through (b)(3)(v) of this section, such as public health consequences, may be considered in evaluating neurovirulence test results. The virus pool under test is satisfactory for poliovirus vaccine only if at least 80 percent of the animals in each group survive the observation period and if a comparative analysis of the test results demonstrates that the neurovirulence of the test virus pool does not exceed that of the Reference Attenuated Poliovirus, Type 1.

(4) *Test with Reference Attenuated Poliovirus.* The Reference Attenuated Poliovirus, Type 1, shall be tested as prescribed in paragraphs (b)(1) and (b)(2) of this section at least once for every 10 production lots of vaccine, except that the interval between the test of the reference and the test of any lot of vaccine shall not be greater than 3 months. The test procedure shall be considered acceptable only if lesions of poliomyelitis are seen in monkeys inoculated with the reference material at a frequency statistically compatible with all previous tests with this preparation.

§ 630.18 Additional tests for safety.

(a) *Tests prior to filtration.* Monovalent virus pools shall contain no demonstrable viable microbial agent, except for unavoidable bacteriophage and the intended attenuated live poliovirus. The vaccine shall be tested for the absence of other infectious agents, including polioviruses of other types or strains. Testing of each monovalent pool shall include the following procedures:

(1) *Inoculation of rabbits.* A minimum of 100 milliliters of each monovalent virus pool shall be tested by inoculation into at least 10 healthy rabbits, each weighing 1,500 to 2,500 grams. Each rabbit shall be injected with a total of 1.0 milliliter intradermally in multiple sites, and subcutaneously with 9.0 milliliters, of the monovalent virus pool and the animals observed for at least 3 weeks. Each rabbit that dies after the first 24 hours of the test, or is sacrificed because of illness, shall be necropsied and the brain and organs removed and examined. The monovalent virus pool may be used for poliovirus vaccine only if at least 80 percent of the rabbits remain healthy and survive the entire period and if all the rabbits used in the test fail to show lesions of any kind at the sites of inoculation and fail to show evidence of cercopithecid herpesvirus 1 or any other viral infection.

(2) *Inoculation of adult mice.* Each of at least 20 adult mice, each weighing 15 to 20 grams, shall be inoculated intraperitoneally with 0.5 milliliter and intracerebrally with 0.03 milliliter of each monovalent virus pool. The mice shall be observed for 21 days. Each mouse that dies after the first 24 hours of the test, or is sacrificed because of illness, shall be necropsied and

examined for evidence of viral infection by direct observation and subinoculation of appropriate tissue into at least five additional mice which shall be observed for 21 days. The monovalent virus pool may be used for poliovirus vaccine only if at least 80 percent of the mice remain healthy and survive the entire period and if all the mice used in the test fail to show evidence of lymphocytic choriomeningitis virus or other viral infection.

(3) *Inoculation of suckling mice.* Each of at least 20 suckling mice less than 24 hours old shall be inoculated intracerebrally with 0.01 milliliter and intraperitonally with 0.1 milliliter of the monovalent virus pool. The mice shall be observed daily for at least 14 days. Each mouse that dies after the first 24 hours of the test, or is sacrificed because of illness, shall be necropsied and examined for evidence of viral infection. Such examination shall include subinoculation of appropriate tissue suspensions into an additional group of at least five suckling mice by the intracerebral and intraperitoneal routes and observed daily for 14 days. In addition, a blind passage shall be made of a single pool of the emulsified tissue (minus skin and viscera) of all mice surviving the original 14–day test. The monovalent virus pool may be used for poliovirus vaccine only if at least 80 percent of the mice remain healthy and survive the entire period and if all the mice used in the test fail to show evidence of Coxsackie or other viral infection.

(4) *Inoculation of guinea pigs.* Each of at least five guinea pigs, each weighting 350 to 450 grams, shall be inoculated intracerebrally with 0.1 milliliter and intraperitoneally with 5.0 milliliters on the monovalent virus pool to be tested. The animals shall be observed for at least 42 days and rectal temperatures recorded daily for the last 3 weeks of the test. Each animal that dies after the first 24 hours of the test, or is sacrificed because of illness, shall be necropsied and its tissues shall be examined both microscopically and culturally for evidence of tubercle bacilli, and by passage of tissue suspensions into at least three other guinea pigs by the intracerebral and intraperitoneal routes of inoculation for evidence of viral infection. If clinical signs suggest infection with lymphocytic choriomeningitis virus, serological tests shall be performed on blood samples of the test guinea pigs to confirm the clinical observations. Animals that die or are sacrificed during the first 3 weeks after inoculation with the monovalent virus pools shall be examined for infection with lymphocytic choriomeningitis virus. Animals that die in the final 3 weeks shall be examined both microscopically and culturally for *Mycobacterium tuberculosis.* The monovalent virus pool may be used for poliovirus vaccine only if at least 80 percent of all animals remain healthy and survive the observation period and if all the animals used in the test fail to show evidence of infection with *Mycobacterium tuberculosis* or any viral infection.

(5) *Inoculation of monkey kidney tissue cultures.* At least 500 doses or 50 milliliters, whichever is a greater volume of virus, taken either from each undiluted monovalent virus pool or, in equal proportions from individual harvests or subpools, shall be tested for simian viruses in Macaca monkey kidney tissue cultures and, in the same volume, in Cercopithecus monkey kidney tissue cultures. A dilution of the virus pool in medium not to exceed 1:4 shall be used. The area of surface growth of the cells shall be at least 3 square centimeters per milliliter of test inoculum. The test poliovirus shall be neutralized by high-titer specific antiserum of nonprimate origin. The immunizing antigens used for the preparation of antisera shall be grown in a cell line other than the cell line used for testing the vaccine. The cultures shall be observed for at least 14 days. At the end of the observation period at least one subculture of fluid from the Cercopithecus kidney cell culture shall be made in the same tissue culture system and the subculture shall be observed for at least 14 days. The monovalent virus pool may be used for poliovirus vaccine only if all the tissue cultures fail to show evidence of the presence of simian viruses or any other viral infection.

(6) *Inoculation of human cell cultures.* At least 500 doses or 50 milliliters, whichever represents a greater volume of virus, taken from either a single

monovalent pool or, in equal proportions from individual harvests or subpools, shall be tested for the presence of measles virus in either:

(i) Primary human amnion cells,

(ii) Primary human kidney cells, or

(iii) Any other human or nonhuman cell system of comparable suspectibility to unmodified measles virus.

The virus pool shall be diluted with medium not to exceed 1:4. The area of surface growth of cells shall be at least 3 square centimeters per milliliter of test inoculum. The test material shall be neutralized with poliovirus antiserum of other than primate origin if the tissue culture cell system used is susceptible to poliovirus. The immunizing antigens used for the preparation of antiserum shall be grown in a cell line other than the cell line used for testing the vaccine. The culture shall be observed for at least 14 days. The monovalent virus pool may be used for poliovirus vaccine only if all tissue cultures fail to show evidence of the presence of measles virus or any other viral infection.

(7) *Inoculation of a rabbit kidney tissue culture.* At least 500 milliliters of virus pool, taken from either a single monovalent pool or in equal proportions from individual harvests or subpools, shall be tested in primary rabbit kidney tissue culure preparations for evidence of cercopithecid herpesvirus 1. The virus pool shall be diluted with medium not to exceed 1:4. The area of surface growth of cells shall be at least 3 square centimeters per milliliter of test inoculum. The culture shall be observed for at least 14 days. The monovalent virus pool may be used for poliovirus vaccine only if all tissue cultures fail to show evidence of the presence of herpesvirus.

(b) *Tests for in vitro markers.* In addition to the neurovirulence test required by §§ 630.16 or 630.17, the following tests relating to safety shall be performed on each monovalent virus pools after the filtration process. Tests shall be performed on each monovalent virus pool using the marker tests described below or other methods shown to be of comparable value in indentification of the attenuated strain. The test results shall demonstrate that the monovalent virus pool under test and the seed virus have substantially the same marker characteristics.

(1) *rct/40 Marker.* Attenuated strains which grow readily at 40 °C (±0.5 °C) are classified as rct/40 positive (+) in contrast to the rct/40 negative (−) strains, which show an increased growth of at least 100,000 fold at 36 °C over that obtained at 40 °C. Comparative determinations shall be made in suitable culture vessels. ≤

(2) *d Marker.* Attenuated strains which grow readily at low concentrations of bicarbonate under agar are classified as d positive (+) in contrast to the d negative (−) strains, which exhibit delayed growth under the same conditions. The cultures shall be grown in a 36 °C incubator, in suitable culture vessels in an environment of 5 percent CO_2 in air.

(c) *Final container sterility test.* The final container sterility test need not be performed provided aseptic techniques are used in the filling process.

[56 FR 21432, May 8, 1991; 56 FR 27787, June 17, 1991]

§630.19 General requirements.

(a) *Vaccine release.* No lot of trivalent vaccine shall be released by the manufacturer unless each monovalent virus pool contained therein:

(1) Has been manufactured by the same procedures;

(2) Has met the criteria of neurovirulence for monkeys prescribed in §§ 630.16(b) or 630.17(b);

(3) Has met the criteria of in vitro markers prescribed in §630.18(b); and

(4) Has been released for further manufacturing by the Director, Center for Biologics Evaluation and Research unless, at the Director's discretion, the Director determines that lot release by the Center for Biologics Evaluation and Research is not required. The protocols for all monovalent virus pools produced sequentially from the same seed and tested, in whole or in part, in accordance with §§630.16(b) or 630.17(b) shall be submitted to the Director, Center for Biologics Evaluation and Research, whether or not release of the pool for further manufacturing is requested. For monovalent virus pools not tested under §§630.16(b) or 630.17(b),

the manufacturer shall report the reasons for partial manufacture to the Director, Center for Biologics Evaluation and Research.

(b) *Labeling.* In addition to the items required by other applicable labeling provisions of this chapter, the final container label shall bear a statement indicating that liquid vaccine may not be used for more than 7 days after opening the container. Labeling may include a statement indicating that, for frozen vaccine, a maximum of 10 freeze-thaw cycles is permissible provided the total cumulative duration of thaw does not exceed 24 hours, and provided the temperature does not exceed 8 °C during the periods of thaw.

(c) *Samples and protocols.* For each trivalent lot of vaccine and for each monovalent virus pool, the following materials shall be submitted in accordance with instructions received from the Director, Center for Biologics Evaluation and Research, 8800 Rockville Pike, Bethesda, MD 20892.

(1) A protocol that consists of a summary of the history of manufacture of each trivalent lot or monovalent virus pool, including any test results requested by the Director, Center for Biologics Evaluation and Research.

(2) Twenty milliliters of monovalent virus pool before filtration.

(3) Forty milliliters of monovalent virus pool after filtration. The titer of the sample shall be no less than the equivalent of $10^{7.5}$ $TCID_{50}$ per milliliter when titrated in HEp–2 cells; if the titer is greater than $10^{7.5}$ $TCID_{50}$ per milliliter, a correspondingly smaller volume may be submitted.

(4) A total of at least 50 single doses or the equivalent thereof of the trivalent vaccine.

(5) When deemed appropriate, the Director, Center for Biologics Evaluation and Research, may require submission of samples or sample volumes other than those specified in paragraphs (c)(2), (c)(3), and (c)(4) of this section.

(d) *Public health implications.* In interpreting any provision of the regulations governing oral poliovirus vaccine, the agency may consider any potential effect on individual or public health, including effects related to vaccine supply.

(e) *Alternative procedures.* (1) The Director, Center for Biologics Evaluation and Research, may approve an exception or alternative to any requirement in subpart B of part 630 regarding Poliovirus Vaccine Live Oral. Requests for such exceptions or alternatives should ordinarily be made in writing. However, in limited circumstances such requests may be made orally and permission may be given orally by the Director, Center for Biologics Evaluation and Research. Oral requests and approvals must be followed by written requests and written approvals.

(2) FDA will publish a list of approved alternative procedures and exceptions periodically in the FEDERAL REGISTER.

(f) *Status of vaccine in distribution.* Poliovirus Vaccine Live Oral released or in distribution prior to May 8, 1991, is deemed to meet the requirements of supart B of part 630.

Subpart C—[Reserved]

Subpart D—Measles Virus Vaccine Live

§ 630.30 Measles Virus Vaccine Live.

(a) *Proper name and definition.* The proper name of this product shall beMeasles Virus Vaccine Live, which shall consist of a preparation of live, attenuated, measles virus.

(b) *Criteria for acceptable strains of attenuated measles virus.* Strains of attenuated measles virus used in the manufacture of vaccine shall be identified by (1) historical records, including origin and manipulation during attenuation and (2) antigenic specificity as measles virus as demonstrated by tissue culture neutralization tests. Strains used for the manufacture ofMeasles Virus Vaccine Live, shall have been shown to be safe and potent in man by field studies with experimental vaccines. The vaccine shall have been demonstrated as safe and potent in at least 10,000 susceptible persons. Susceptibility shall be shown by the absence of neutralizing or other antibodies against measles virus, or by other appropriate methods. Seed virus used for vaccine manufacture shall be free of all demonstrable extraneous

viable microbial agents except for unavoidable bacteriophage.

(c) *Neurovirulence safety test of the virus seed strain in monkeys*—(1) *The test.* A demonstration shall be made in monkeys of the lack of neurotropic properties of the seed strain of attenuated measles virus used in the manufacture of measles virus vaccine. For this purpose and to establish consistency of manufacture of the vaccine, vaccine from each of five consecutive lots shall be tested separately in the following manner:

(i) Samples of each of the five lots of vaccine shall be tested in measles susceptible monkeys. Immediately prior to initiation of a test each monkey shall have been shown to be serologically negative for neutralizing antibodies by means of a tissue culture neutralization test with undiluted serum from each monkey tested at approximately 100 $TCID_{50}$ of Edmonston strain measles virus, or negative for measles virus antibodies as demonstrated by tests of equal sensitivity.

(ii) A test sample of vaccine removed after clarification but before final dilution for standardization of virus content shall be used for the test.

(iii) Vaccine shall be injected by combined intracerebral, intraspinal, and intramuscular routes into not less than 20 Macaca or Cercopithecus monkeys or a species found by the Director, Center for Biologics Evaluation and Research, to be equally suitable for the purpose. The animals shall be in overt good health and injected under deep barbiturate anesthesia. The intramuscular injection shall consist of 1.0 milliliter of test sample into the right leg muscles. At the same time, 200 milligrams of cortisone acetate shall be injected into the left leg muscles, and 1.0 milliliter of procaine penicillin (300,000 units) into the right arm muscles. The intracerebral injection shall consist of 0.5 milliliter of test sample into each thalamic region of each hemisphere. The intraspinal injection shall consist of 0.5 milliliter of test sample into the lumber spinal cord enlargement.

(iv) The monkeys shall be observed for 17–21 days and symptoms of paralysis as well as other neurologic disorders shall be recorded.

(v) At least 90 percent of the test animals must survive the test period without losing more than 25 percent of their weight except that, if at least 70 percent of the test animals survive the first 48 hours after injection, those animals which do not survive this 48-hour test period may be replaced by an equal number of qualified test animals which are tested pursuant to paragraphs (c)(1)(i) through (iv) of this section. At least 80 percent of the injected animals surviving beyond the first 48 hours must show gross or microscopic evidence of inoculation trauma in the thalamic area and microscopic evidence of inoculation trauma in the lumbar region of the spinal cord. If less than 70 percent of the test animals survive the first 48 hours, or if less than 80 percent of the animals meet the inoculation criteria prescribed in this paragraph, the test must be repeated.

(vi) At the end of the observation period, each surviving monkey shall (*a*) be bled and the serum tested for evidence of serum antibody conversion to measles virus and (*b*) be autopsied and samples of cerebral cortex and of cervical and lumbar spinal cord enlargements shall be taken for virus recovery and identification if needed pursuant to paragraph (c)(1)(vii) of this section. Histological sections shall be prepared from both spinal cord enlargements and appropriate sections of the brain and examined.

(vii) Doubtful histopathological findings necessitate (*a*) examination of a sample of sections from several regions of the brain in question, and (*b*) attempts at virus recovery from the nervous systems tissues previously removed from the animal.

(viii) The lot is satisfactory if the histological and other studies demonstrate no evidence of changes in the central nervous system attributable to unusual neurotropism of the seed virus or of the presence of extraneous neurotropic agents.

(2) *Wild virus controls.* As a check against the inadvertent introduction of wild measles virus, at least four uninoculated measles susceptible control monkeys shall be maintained as either cage mates to, or within the same immediate area of, the 20 inoculated test animals for each lot of vaccine for

the entire period of observation (17–21 days) and an additional 10 days. Serum samples from these control contact monkeys drawn at the time of seed virus inoculation of the test animals, and again after completion of the test, shall be shown to be free of measles neutralizing antibodies.

(3) *Test results.* (i) For each lot of vaccine under test, at least 80 percent of the monkeys must show measles antibody serological conversion (1:4 or greater) when the serum as obtained from the monkey is tested and the control contact monkeys must demonstrate no immunological response indicative of measles virus infection.

(ii) The measles virus seed has acceptable neurovirulence properties for use in vaccine manufacture only if for each of the five lots (*a*) 90 percent of the monkeys survive the observation period, (*b*) the histological and other studies produce no evidence of changes in the central nervous system attributable to unusual neurotropism of the seed virus, and (*c*) there is no evidence of the presence of extraneous neurotropic agents.

(4) *Need for additional neurovirulence safety testing.* A neurovirulence safety test as prescribed in this paragraph shall be performed on vaccine from five consecutive lots whenever a new production seed lot is introduced or whenever the source of cell culture substrate must be reestablished and recertified as prescribed in §630.32(a) and (b) of this part.

[38 FR 32068, Nov. 20, 1973, as amended at 40 FR 11719, Mar. 13, 1975; 49 FR 23834, June 8, 1984; 50 FR 4138, Jan. 29, 1985; 55 FR 11013, Mar. 26, 1990; 55 FR 47875, Nov. 16, 1990]

§630.31 Clinical trials to qualify for license.

To qualify for license, the antigenicity of the vaccine shall have been determined by clinical trials of adequate statistical design, by a suitable route of administration of the product. Such clinical trials shall be conducted with five lots of measles virus vaccine which have been manufactured by the same methods. There shall be a demonstration under circumstances in which adequate clinical and epidemiological surveillance of illness has been maintained to show that the measles virus vaccine, when administered as recommended by the manufacturer, is free of harmful effect upon administration to approximately 1,000 susceptible individuals, in that there were no detectable neutralizing antibodies before vaccination and there was serological conversion after vaccination. The five lots of vaccine shall be distributed as evenly as possible among the 1,000 individuals tested. Demonstration shall be made of immunogenic effect by the production of specific measles neutralizing antibodies (i.e., sero-conversion from less than 1:4 to 1:8 or greater) in at least 90 percent of each of five groups of measles susceptible individuals, each having received a virus vaccine dose which is not greater than that which was demonstrated to be safe in field studies (§630.30(b)) when used under comparable conditions. Such clinical trials shall be conducted in compliance with part 56 of this chapter unless exempted under §56.104 or granted a waiver under §56.105, and with the requirements for informed consent set forth in part 50 of this chapter.

[55 FR 47875, Nov. 16, 1990]

§630.32 Manufacture of live, attenuated Measles Virus Vaccine.

(a) *Virus cultures.* Virus shall be propagated in chick embryo tissue cultures.

(b) *Virus propagated in chick embryo tissue cultures.* Embryonated chicken eggs used as the source of chick embryo tissue for the propagation of measles virus shall be derived from flocks certified to be free of Salmonella pullorum, avian tuberculosis, fowl pox, Rous sarcoma, avian leucosis, reticuloendotheliosis virus, and other adventitious agents pathogenic for chickens. If eggs are procured from flocks that are not so certified, tests shall be performed to demonstrate freedom of the vaccine from such agents. (See §630.35(a)(8) for test for avian leucosis.)

(c) [Reserved]

(d) *Passage of virus strain in vaccine manufacture.* Virus in the final vaccine shall represent no more than ten tissue culture passages beyond the passage used to perform the clinical trials (§630.30(b)) which qualified the manufacturer's vaccine strain for license.

(e) *Tissue culture preparation.* Only primary cell tissue cultures shall be used in the manufacture of Measles Virus Vaccine. Continuous cell lines shall not be introduced or propagated in Measles Virus Vaccine manufacturing areas.

(f) *Control vessels.* (1) From the tissue used for the preparation of tissue cultures for growing attenuated measles virus, an amount of processed cell suspension equivalent to that used to prepare 500 ml. of tissue culture shall be used to prepare uninfected tissue control materials. This material shall be distributed in control vessels and observed microscopically for a period of no less than 14 days beyond the time of inoculation of the production vessels with measles virus; but if the production vessels are held for use in vaccine manufacture for more than 14 days, the control vessels shall be held and observed for the additional period. At the end of the observation period or at the time of virus harvest, whichever is later, fluids from the control cultures shall be tested for the presence of adventitious agents as follows:

Samples of fluid from each control vessel shall be collected at the same time as fluid is harvested from the corresponding production vessels. If multiple virus harvests are made from the same cell suspension, the control samples for each harvest shall be frozen and stored at −60° C. until the last viral harvest for that cell suspension is completed. The fluid from all the control samples from that suspension shall be pooled in proportionate amounts and at least five ml. inoculated into human and simian cell tissue culture systems and in the tissue culture system used for virus production. The cultures shall be observed for the presence of changes attributable to growth of adventitious viral agents including hemadsorption viral agents.

(2) The cell sheets of one quarter to one third of the control vessels shall be examined at the end of the observation period (14 days or longer) for the presence of hemadsorption viruses by the addition of guinea pig red blood cells. If the chick embryo cultures were not derived from a certified source (paragraph (b) of this section), the remaining tissue culture controls may be used to test for avian leucosis virus using either Rubin's procedure for detecting Resistance Inducing Factor (RIF) or a method of equivalent effectiveness.

(3) The test is satisfactory only if there is no evidence of adventitious viral agents and if at least 80 percent of the control vessels are available for observation at the end of the observation period (14 days or longer).

(g) *Test samples.* Samples of virus harvests or pools for testing by inoculation into animals, into tissue culture systems, into embryonated hens' eggs, and into bacteriological media, shall be withdrawn immediately after harvesting or pooling but prior to freezing except that samples of test materials frozen immediately after harvesting or pooling and maintained at −60° C. or below, may be tested upon thawing, provided no more than two freeze-thaw cycles are employed. The required tests shall be initiated without delay after thawing.

[38 FR 32068, Nov. 20, 1973, as amended at 40 FR 11719, Mar. 13, 1975; 47 FR 24699, June 8, 1982]

§ 630.33 Reference virus.

A U.S. Reference Measles Virus, Live, Attenuated, shall be obtained from the Center for Biologics Evaluation and Research as a control for correlation of virus titers.

[38 FR 32068, Nov. 20, 1973, as amended at 49 FR 23834, June 8, 1984; 55 FR 11013, Mar. 26, 1990]

§ 630.34 Potency test.

The concentration of live measles virus shall constitute the measure of potency. The titration shall be performed in a suitable cell culture system, free of wild viruses, using either the U.S. Reference Measles Virus, Live, Attenuated or a calibrated equivalent strain as a titration control. The concentration of live measles virus contained in the vaccine of each lot under test shall be no less than the equivalent of 1,000 $TCID_{50}$ of the U.S. reference per human dose.

§ 630.35 Test for safety.

(a) *Tests prior to clarification of vaccine manufactured in chick embryo tissue cultures.* Prior to clarification, the following tests shall be performed on each virus pool of chick embryo tissue culture:

(1) *Inoculation of adult mice.* Each of at least 20 adult mice each weighing 15–20 grams shall be inoculated intraperitoneally with 0.5 ml. and intracerebrally with 0.03 ml. amounts of each virus pool to be tested. The mice shall be observed for 21 days. Each mouse that dies after the first 24 hours of the test, or is sacrificed because of illness, shall be necropsied and examined for evidence of viral infection by direct observation and subinoculation of appropriate tissue into at least five additional mice which shall be observed for 21 days. The virus pool may be used only if at least 80 percent of the original group of mice remain healthy and survive the observation period and if none of the mice show evidence of a transmissible agent or other viral infection, other than measles virus, attributable to the vaccine.

(2) *Inoculation of suckling mice.* Each of at least 20 suckling mice less than 24 hours old shall be inoculated intracerebrally with 0.01 ml. and intraperitoneally with 0.1 ml. of the virus pool to be tested. The mice shall be observed daily for at least 14 days. Each mouse that dies after the first 24 hours of the test, or is sacrificed because of illness, shall be necropsied and examined for evidence of viral infection. Such examination shall include subinoculation of appropriate tissue suspensions into an additional group of at least five suckling mice by intracerebral and intraperitoneal routes and observed daily for 14 days. In addition, a blind passage shall be made of a single pool of the emulsified tissue (minus skin and viscera) of all mice surviving the original 14-day test. The virus pool is satisfactory for Measles Virus Vaccine only if at least 80 percent of the original inoculated mice remain healthy and survive the entire observation period, and if none of the mice used in the test show evidence of a transmissible agent or viral infection, other than measles virus, attributable to the vaccine.

(3) *Inoculation of monkey tissue cell cultures.* A volume of virus suspension of each undiluted virus pool, equivalent to at least 500 human doses or 50 milliliters, whichever represents a greater volume, shall be tested for adventitious agents in *Cercopithecus* monkey kidney tissue culture preparations or *Erythrocebus patas* monkey kidney tissue culture preparations, after neutralization of the measles virus by a high titer antiserum of nonhuman, nonsimian and nonchicken origin. The immunizing antigen used for the preparation of the measles antiserum shall be grown in tissue culture cells that shall be free of extraneous viruses which might elicit antibodies that could inhibit growth of extraneous viruses present in the measles virus pool. The tissue culture of the virus pool shall be observed for no less than 14 days. The virus pool is satisfactory for measles virus vaccine only if all the tissue culture tests fail to show evidence of any extraneous transmissible agent other than measles virus attributable to the vaccine.

(4) *Inoculation of other cell cultures.* The measles virus pool shall be tested in the same manner as prescribed in paragraph (a)(3) of this section in rhesus or cynomolgus monkey kidney, chick embryo, and human tissue cell cultures.

(5) *Inoculation of embryonated chicken eggs.* A volume of virus suspension of each undiluted virus pool, equivalent to at least 100 doses or 10 milliliters, whichever represents a greater volume, after neutralization of the measles virus by a high titer antiserum of nonhuman, nonsimian, nonavian origin shall be tested as follows:

(i) Embryonated eggs, 10 to 11 days old, shall be inoculated by the allantoic route using 0.5 milliliter per egg. Follow incubation at 35° C for 72 hours, the allantoic fluids shall be harvested, pooled, and subpassed by the same route into fresh, embryonated eggs, 10 to 11 days old, using 0.5 milliliter per egg and incubated at 35° C for 72 hours. Both the initial pool and the subpassage harvest shall be tested for the presence of hemagglutinin. The virus pool is satisfactory if the embryos appear normal and there is no evidence of hemagglutinating agents.

(ii) Embryonated eggs, 6 to 7 days old, shall be inoculated by the yolk sac route using 0.5 milliliter per egg. Following incubation at 35° C for at least 9 days, the yolk sacs shall be harvested and pooled. A 10-percent suspension of

yolk sacs shall be subpassed by the same route into fresh embryonated eggs, 6 to 7 days old, using 0.5 milliliter of inoculum per egg and incubated at 35° C for at least 9 days. The virus pool is satisfactory if the embryos in both the initial test and the subpassage appear normal.

(6) [Reserved]

(7) *Bacteriological tests.* Each virus pool shall be tested for sterility in accordance with §610.12 of this chapter. In addition each virus pool shall be tested for the presence of M. tuberculosis, both avian and human, by appropriate culture methods.

(8) *Test for avian leucosis.* If the cultures were not derived from a certified source (§630.32(b)), and the control fluids were not tested for avian leucosis (§630.32(f)), at least 500 doses or 50 ml., whichever represents a greater volume of each undiluted vaccine pool, shall be tested and found negative for avian leucosis, using either Rubin's procedure for detecting Resistance Inducing Factor (RIF) or another method of equivalent effectiveness.

(b) [Reserved]

(c) *Clarification.* After harvesting and removal of samples for testing as prescribed above in this section, the virus fluids shall be clarified by centrifugation, by passage through filters of sufficiently small porosity, or by any other method that will assure removal of all intact tissue cells which may have been collected in the harvesting process.

[38 FR 32068, Nov. 20, 1973, as amended at 40 FR 11719, Mar. 13, 1975; 41 FR 43400, Oct. 1, 1976; 47 FR 24699, June 8, 1982]

§ 630.36 General requirements.

(a) *Final container tests.* In addition to the tests required pursuant to §610.14 of this chapter, an immunological and virological identity test shall be performed on the final container if it was not performed on each pool or the bulk vaccine prior to filling.

(b)—(c) [Reserved]

(d) *Dose.* These standards are based on an individual human immunizing dose of no less than 1,000 $TCID_{50}$ of Measles Virus Vaccine Live, expressed in terms of the assigned titer of the U.S. reference measles virus.

(e) *Labeling.* In addition to the items required by other applicable labeling provisions of this subchapter, single-dose container labeling for vaccine which is not protected against photochemical deterioration shall include a statement cautioning against exposure to sunlight.

(f) [Reserved]

(g) *Photochemical deterioration; protection.* Vaccine in multiple dose final containers shall be protected against photochemical deterioration. Such containers may be colored, or outside coloring or protective covering may be used for this purpose, provided (1) the method used is shown to provide the required protection, and (2) visible examination of the contents is not precluded. Vaccine in single dose containers may be protected in the same manner provided the same conditions are met.

(h) *Sample and protocols.* The following materials shall be submitted to the Director, Center for Biologics Evaluation and Research, Food and Drug Administration, 8800 Rockville Pike, Bethesda, MD 20892:

(1) For each lot of vaccine:

(i) A protocol which consists of a summary of the history of the manufacture of the lot, including all results of each test for which test results are requested by the Director, Center for Biologics Evaluation and Research.

(ii) A total of no less than two 25-milliliter volumes in a frozen state (−60° C) of preclarification bulk vaccine containing no preservative or adjuvant.

(iii) A total of no less than 30 containers of the vaccine from each filling of each bulk lot of single-dose containers. A total of no less than six 50-dose containers or ten 10-dose containers of the vaccine from each filling of each bulk lot of multiple-dose containers.

(2) In addition to the requirements of paragraph (h)(1) of this section, whenever a new production seed lot is introduced, or whenever the source of cell culture substrate must be reestablished and recertified, samples consisting of no less than 100 milliliters in 10 milliliter volumes, in a frozen state (−60° C), of postclarification bulk vaccine

containing stabilizer but no preservative or adjuvant, taken from each of 5 consecutive lots of the bulk vaccine.

[38 FR 32068, Nov. 20, 1973, as amended at 41 FR 10429, Mar. 11, 1976; 49 FR 23834, June 8, 1984; 50 FR 4138, Jan. 29, 1985; 51 FR 15610, Apr. 25, 1986; 55 FR 11013, Mar. 26, 1990]

Subpart E—[Reserved]

Subpart F—Mumps Virus Vaccine Live

§ 630.50 Mumps Virus Vaccine Live.

(a) *Proper name and definition.* The proper name of this product shall be Mumps Virus Vaccine Live, which shall consist of a preparation of live, attenuated mumps virus.

(b) *Criteria for acceptable strains of attenuated mumps virus.* Strains of attenuated mumps virus used in the manufacture of vaccine shall be identified by (1) historical records including origin and manipulation during attenuation, (2) antigenic specificity as mumps virus as demonstrated by tissue culture neutralization tests. Strains used for the manufacture of Mumps Virus Vaccine Live shall have been shown to be safe and potent in at least 5,000 susceptible individuals by field studies with experimental vaccines. Susceptibility shall be shown by the absence of neutralizing or other antibodies against mumps virus, or by other appropriate methods. Seed virus used for vaccine manufacture shall be free of all demonstrable extraneous viable microbial agents except for unavoidable bacteriophage.

(c) *Neurovirulence safety test of the virus seed strain in monkeys*—(1) *The test.* A demonstration shall be made in monkeys of the lack of neurotropic properties of the seed strain of attenuated mumps virus used in the manufacture of mumps vaccine. For this purpose and to establish consistency of manufacture of the vaccine, vaccine from each of five consecutive lots shall be tested separately in monkeys shown to be serologically negative for mumps virus antibodies in the following manner:

(i) A test sample of vaccine removed after clarification but before final dilution for standardization of virus content shall be used for the test.

(ii) Vaccine shall be injected by combined intracerebral, intraspinal, and intramuscular routes into not less than 20 Macaca or Cercopithecus monkeys or a species found by the Director, Center for Biologics Evaluation and Research, to be equally suitable for the purpose. The animals shall be in overt good health and injected under deep barbiturate anesthesia. The intramuscular injection shall consist of 1.0 milliliter of test sample into the right leg muscles. At the same time, 200 milligrams of cortisone acetate shall be injected into the left leg muscles, and 1.0 milliliter of procaine penicillin (300,000 units) into the right arm muscles. The intracerebral injection shall consist of 0.5 milliliter of test sample into each thalamic region of each hemisphere. The intraspinal injection shall consist of 0.5 milliliter of test sample into the lumbar spinal cord enlargement.

(iii) The monkeys shall be observed for 17–21 days and symptoms of paralysis as well as other neurologic disorders shall be recorded.

(iv) At least 90 percent of the test animals must survive the test period without losing more than 25 percent of their weight except that, if at least 70 percent of the test animals survive the first 48 hours after injection, those animals which do not survive this 48-hour test period may be replaced by an equal number of qualified test animals which are tested pursuant to paragraphs (c)(1)(i) through (iii) of this section. At least 80 percent of the injected animals surviving beyond the first 48 hours must show gross or microscopic evidence of inoculation trauma in the thalamic area and microscopic evidence of inoculation trauma in the lumbar region of the spinal cord. If less than 70 percent of the test animals survive the first 48 hours, or if less than 80 percent of the animals meet the inoculation criteria prescribed in this paragraph, the test must be repeated.

(v) At the end of the observation period, each surviving animal shall be autopsied and samples of cerebral cortex and of cervical and lumbar spinal cord enlargements shall be taken for virus recovery and identification if

needed pursuant to paragraph (c)(1) (vi) of this section. Histological sections shall be prepared from both spinal cord enlargements and appropriate sections of the brain and examined.

(vi) Doubtful histopathological findings necessitate (*a*) examination of a sample of sections from several regions of the brain in question, and (*b*) attempts at virus recovery from the nervous system tissues previously removed from the animals.

(vii) The lot is satisfactory if the histological and other studies demonstrate no evidence of changes in the central nervous system attributable to unusual neurotropism of the seed virus or of the presence of extraneous neurotropic agents.

(2) *Test results.* The mumps virus seed has acceptable neurovirulence properties for use in vaccine manufacture only if for each of the five lots (i) 90 percent of the monkeys survive the observation period, (ii) the histological and other studies produce no evidence of changes in the central nervous system attributable to unusual neurotropism or replication of the seed virus and (iii) there is no evidence of the presence of extraneous neurotropic agents.

(3) *Need for additional neurovirulence safety testing.* A neurovirulence safety test as prescribed in this paragraph shall be performed on vaccine from five consecutive lots whenever a new production seed lot is introduced or whenever the source of cell culture substrate must be reestablished and recertified as prescribed in §630.52(a).

[38 FR 32068, Nov. 20, 1973, as amended at 49 FR 23834, June 8, 1984; 50 FR 4138, Jan. 29, 1985; 55 FR 11013, Mar. 26, 1990; 55 FR 47875, Nov. 16, 1990]

§630.51 Clinical trials to qualify for license.

To qualify for license, the antigenicity of Mumps Virus Vaccine Live shall be determined by clinical trials, conducted in compliance with part 56 of this chapter unless exempted under §56.104 or granted a waiver under §56.105, and with part 50 of this chapter, that follow the procedures prescribed in §630.31, except that the immunogenic effect shall be demonstrated by establishing that a protective antibody response has occurred in at least 90 percent of each of the five groups of mumps-susceptible individuals, each having received the parenteral administration of a virus vaccine dose not greater than that demonstrated to be safe in field studies (§630.50(b)) when used under comparable conditions.

[46 FR 8956, Jan. 27, 1981, as amended at 50 FR 4138, Jan. 29, 1985]

§630.52 Manufacture of Mumps Virus Vaccine Live

(a) *Virus cultures.* Mumps virus shall be propagated in chick embryo cell cultures. The embryonated chicken eggs used as the source of chick embryo tissue for the propagation of mumps virus shall be derived from flocks certified or tested as prescribed in §630.32(b).

(b) *Passage of virus strain in vaccine manufacture.* Virus in the final vaccine shall represent no more than five cell culture passages beyond the passage used to perform the clinical trials (§630.50(b)) which qualified the manufacturer's vaccine strain for license.

(c) *Cell culture preparation.* Only primary cell cultures shall be used in the manufacture of mumps virus vaccine. Continuous cell lines shall not be introduced or propagated in mumps virus vaccine manufacturing areas.

(d) *Control vessels.* From the tissue used for the preparation of cell cultures for growing attenuated mumps virus, an amount of processed cell suspension equivalent to that used to prepare 500 ml. of cell culture shall be used to prepare uninfected tissue control materials which shall be prepared and tested by following the procedures prescribed in §630.32(f).

(e) *Test samples.* Test samples of mumps virus harvests or pools shall be withdrawn and maintained by following the procedures prescribed in §630.32(g).

[38 FR 32068, Nov. 20, 1973, as amended at 50 FR 4138, Jan. 29, 1985]

§630.53 Reference virus.

An NIH Reference Mumps Virus, Live, shall be obtained from the Center for Biologics Evaluation and Research

as a control for correlation of virus titers.

[38 FR 32068, Nov. 20, 1973, as amended at 49 FR 23834, June 8, 1984; 55 FR 11013, Mar. 26, 1990]

§ 630.54 Potency test.

The concentration of live mumps virus shall constitute the measure of potency. The titration shall be performed in a suitable cell culture system, free of wild viruses, using either the Reference Mumps Virus, Live, or a calibrated equivalent strain as a titration control. The concentration of live mumps virus contained in the vaccine of each lot under test shall be no less than the equivalent of 5,000 $TCID_{50}$ of the reference virus per human dose.

§ 630.55 Test for safety.

(a) *Tests prior to clarification.* Prior to clarification, the following tests shall be performed on each mumps virus pool prepared in chick embryo cell culture:

(1) *Inoculation of adult mice.* The test shall be performed in the volume and following the procedures prescribed in § 630.35(a)(1), and the virus pool is satisfactory only if equivalent test results are obtained.

(2) *Inoculation of suckling mice.* The test shall be performed in the volume and following the procedures prescribed in § 630.35(a)(2), and the virus pool is satisfactory only if equivalent test results are obtained.

(3) *Inoculation of monkey cell cultures.* A mumps virus pool shall be tested for adventitious agents in the volume and following the procedures prescribed in § 630.35(a)(3), and the virus pool is satisfactory only if equivalent test results are obtained.

(4) *Inoculation of other cell cultures.* The mumps virus pool shall be tested for adventitious agents in the volume and following the procedures prescribed in § 630.35(a)(3), in rhesus or cynomolgus monkey kidney, in whole chick embryo, and in human cell cultures. In addition, each virus pool shall be tested in chick embryo kidney in the same manner except that the volume tested in each cell culture shall be equivalent to 250 human doses or 25 milliliters, whichever represents a greater volume. The mumps virus pool is satisfactory only if results equivalent to those in § 630.35(a)(3) are obtained.

(5) *Inoculation of embryonated chicken eggs.* A neutralized suspension of each undiluted mumps virus pool shall be tested in the volume and following the procedures prescribed in § 630.35(a)(5), and the virus pool is satisfactory only if there is no evidence of adventitious agents.

(6) *Bacteriological tests.* In addition to the tests for sterility required pursuant to § 610.12 of this chapter, bacteriological tests shall be performed on each mumps virus pool for the presence of M. tuberculosis, both avian and human, by appropriate culture methods. The virus pool is satisfactory only if found negative for M. tuberculosis, both avian and human.

(7) *Test for avian leucosis.* If the cultures were not derived from a certified source and control fluids were not tested for avian leucosis, the vaccine shall be tested in the volume and following the procedures prescribed in § 630.35(a)(8). The cultures are satisfactory for vaccine manufacture if found negative for avian leucosis.

(b) *Clarification.* The mumps virus fluids shall be clarified by following the procedures prescribed in § 630.35(c).

[38 FR 32068, Nov. 20, 1973, as amended at 55 FR 47876, Nov. 16, 1990]

§ 630.56 General requirements.

(a) *Final container tests.* In addition to the tests required pursuant to § 610.14 of this chapter, an immunological and virological identity test shall be performed on the final container if it was not performed on each pool or the bulk vaccine prior to filling.

(b) *Dose.* These standards are based on an individual human immunizing dose of no less than 5,000 $TCID_{50}$ of Mumps Virus Vaccine Live, expressed in terms of the assigned titer of the Reference Mumps Virus, Live.

(c) *Labeling.* In addition to the items required by other applicable labeling provisions of this part, single dose container labeling for vaccine which is not protected against photochemical deterioration shall include a statement cautioning against exposure to sunlight.

(d) [Reserved]

(e) *Photochemical deterioration; protection.* Mumps Virus Vaccine Live, in multiple dose containers, shall be protected against photochemical deterioration in accordance with the procedures prescribed in § 630.36(g).

(f) *Samples and protocols.* For each lot of vaccine, the following materials shall be submitted to the Director, Center for Biologics Evaluation and Research, Food and Drug Administration, 8800 Rockville Pike, Bethesda, MD 20892:

(1) A protocol which consists of a summary of the history of manufacture of each lot including all results of each test for which test results are requested by the Director, Center for Biologics Evaluation and Research.

(2) A total of no less than two 25-milliliter volumes, in a frozen state (−60° C), of preclarification bulk vaccine containing no preservative, stabilizer, or adjuvant.

(3) A total of no less than 30 containers of the vaccine from each filling of each bulk lot of single-dose containers. A total of no less than six 50-dose containers or ten 10-dose containers of the vaccine from each filling of each bulk lot of multiple-dose containers.

[38 FR 32068, Nov. 20, 1973, as amended at 39 FR 9661, Mar. 13, 1974; 41 FR 10429, Mar. 11, 1976; 49 FR 23834, June 8, 1984; 50 FR 4138, Jan. 29, 1985; 51 FR 15610, Apr. 25, 1986; 55 FR 11013, Mar. 26, 1990]

Subpart G—Rubella Virus Vaccine Live

§ 630.60 Rubella Virus Vaccine Live.

(a) *Proper name and definition.* The proper name of this product shall be Rubella Virus Vaccine Live, which shall consist of a preparation of live, attenuated rubella virus.

(b) *Criteria for acceptable strains of attenuated rubella virus.* Strains of attenuated rubella virus used in the manufacture of vaccine shall be identified by (1) historical records including origin and manipulation during attenuation and (2) antigenic specificity as rubella virus as demonstrated by tissue culture neutralization tests.

(c) *Extraneous agents.* Seed virus used for vaccine manufacture shall be free of all demonstrable extraneous viable microbial agents except for unavoidable bacteriophage.

(d) *Field studies with experimental vaccines.* (1) Strains used for the manufacture of Rubella Virus Vaccine Live, shall have been shown in field studies with experimental vaccines to be safe and potent in the group of individuals inoculated, which must include at least 10,000 susceptible individuals. Susceptibility shall be shown by the absence of neutralizing or hemagglutination-inhibiting antibodies against rubella virus or by other appropriate methods.

(2) The virus strain used in the field studies shall be propagated in the same cell culture system that will be used in the manufacture of the product.

(3) The field studies shall be so conducted that at least 5,000 of the susceptible individuals must reside when inoculated in areas where health related statistics are regularly compiled in accordance with procedures such as those used by the National Center for Health Statistics. Data in such form as will identify each inoculated person shall be furnished to the Director, Center for Biologics Evaluation and Research.

(4) Inoculated persons shall be shown not to be contagious for contacts through surveillance of rubella susceptible contacts of the inoculated persons.

(e) *Neurovirulence safety test of the virus seed strain in monkeys*—(1) *The test.* A demonstration shall be made in monkeys of the lack of neurotropic properties of the seed strain of attenuated rubella virus used in the manufacture of rubella vaccine. For this purpose and to establish consistency of manufacture of the vaccine, vaccine from each of five consecutive lots shall be tested separately in monkeys shown to be serologically negative for rubella virus antibodies in the following manner:

(i) A test sample of vaccine removed after clarification but before final dilution for standardization of virus content shall be used for the test.

(ii) Vaccine shall be injected by combined intracerebral, intraspinal, and intramuscular routes into not less than 20 Macaca or Cercopithecus monkeys or a species found by the Director, Center for Biologics Evaluation and Research, to be equally suitable for the purpose. The animals shall be in overt

good health and injected under deep barbiturate anesthesia. The intramuscular injection shall consist of 1.0 milliliter of test sample into the right leg muscles. At the same time, 200 milligrams of cortisone acetate shall be injected into the left leg muscles, and 1.0 milliliter of procaine penicillin (300,000 units) into the right arm muscles. The intracerebral injection shall consist of 0.5 milliliter of test sample into each thalamic region of each hemisphere. The intraspinal injection shall consist of 0.5 milliliter of test sample into the lumbar spinal cord enlargement.

(iii) The monkeys shall be observed for 17–21 days and symptoms of paralysis as well as other neurologic disorders shall be recorded.

(iv) At least 90 percent of the test animals must survive the test period without losing more than 25 percent of their weight except that, if at least 70 percent of the test animals survive the first 48 hours after injection, those animals which do not survive this 48-hour test period may be replaced by an equal number of qualified test animals which are tested pursuant to paragraphs (e)(1)(i) through (iii) of this section. At least 80 percent of the injected animals surviving beyond the first 48 hours must show gross or microscopic evidence of inoculation trauma in the thalamic area and microscopic evidence of inoculation trauma in the lumbar region of the spinal cord. If less than 70 percent of the test animals survive the first 48 hours, or if less than 80 percent of the animals meet the inoculation criteria prescribed in this paragraph, the test must be repeated.

(v) At the end of the observation period, each surviving animal shall be autopsied and samples of cerebral cortex and of cervical and lumbar spinal cord enlargements shall be taken for virus recovery and identification if needed pursuant to paragraph (e)(1) (vi) of this section. Histological sections shall be prepared from both spinal cord enlargements and appropriate sections of the brain and examined.

(vi) Doubtful histopathological findings necessitate (*a*) examination of a sample of sections from several regions of the brain in question, and (*b*) attempts at virus recovery from the nervous system tissues previously removed from the animal.

(vii) The lot is satisfactory if the histological and other studies demonstrate no evidence of changes in the central nervous system attributable to the presence of unusual neurotropism of the seed virus or of the presence of extraneous neurotropic agents.

(2) *Test results.* The rubella virus seed has acceptable neurovirulence properties for use in vaccine manufacture only if for each of the five lots: (i) 90 percent of the monkeys survive the observation period, (ii) the histological and other studies produce no evidence of changes in the central nervous system attributable to the presence of unusual neurotropism or replication of the seed virus and (iii) there is no evidence of the presence of extraneous neurotropic agents.

(3) *Need for additional neurovirulence safety testing.* A neurovirulence safety test as prescribed in this paragraph shall be performed on vaccine from five consecutive lots whenever a new production seed lot is introduced or whenever the source of cell culture substrate must be reestablished and recertified as prescribed in §630.62(a), (b) and (d) of this part.

[38 FR 32068, Nov. 20, 1973, as amended at 40 FR 11719, Mar. 13, 1975; 49 FR 23834, June 8, 1984; 50 FR 4138, Jan. 29, 1985; 55 FR 11013, Mar. 26, 1990; 55 FR 47876, Nov. 16, 1990]

§ 630.61 Clinical trials to qualify for license.

To qualify for license, the antigenicity of Rubella Virus Vaccine Live, shall be determined by clinical trials, conducted in compliance with part 56 of this chapter unless exempted under §56.104 or granted a waiver under §56.105, and with part 50 of this chapter, that follow the procedures prescribed in §630.31, except that the immunogenic effect shall be demonstrated by establishing that a protective antibody response has occurred in at least 90 percent of each of the five groups of rubella-susceptible individuals, each having received the parenteral administration of a virus vaccine dose not greater than that demonstrated to be safe in field studies

when used under comparable conditions.

[46 FR 8956, Jan. 27, 1981, as amended at 50 FR 4138, Jan. 29, 1985]

§630.62 Production.

(a) *Virus cultures.* Rubella virus shall be propagated in duck embryo cell cultures, rabbit renal cultures, or in a cell line found by the Director, Center for Biologics Evaluation and Research, to meet the requirements of §610.18(c) of this chapter.

(b) *Virus propagated in duck embryo tissue cell cultures.* Embryonated duck eggs used as a source of duck embryo tissue for the propagation of rubella virus shall be derived from flocks certified to be free of avian tuberculosis, the avian leucosis-sarcoma group of viruses, reticuloendotheliosis virus, and other agents pathogenic for ducks. Only ducks so certified and in overt good health and which are maintained in quarantine shall be used as a source of duck embryo tissue used in the propagation of rubella virus. Ducks in the quarantined flock that die shall be necropsied and examined for evidence of significant pathologic lesions. If any such signs or pathologic lesions are observed, eggs from that flock shall not be used for the manufacture of Rubella Virus Vaccine Live. Control vessels shall be prepared, observed, and tested as prescribed in §630.32(f).

(c) [Reserved]

(d) *Virus propagated in rabbit renal tissue cell cultures.* Only rabbits in overt good health which have been maintained in quarantine individually caged in vermin-proof quarters for a minimum of 6 months, having had no exposure to other rabbits or animals throughout the quarantine period, or rabbits born to rabbits while so quarantined, provided the progency have been kept in the same type of quarantine continuously from birth shall be used as a source of kidney tissue. Animals shall be free of antibodies for agents potentially pathogenic for man unless it has been demonstrated in the license application that the tests required by §630.65(c) to be performed on each lot of vaccine are capable of detecting contamination of agents capable of producing such antibodies.

(1) *Rabbits used for experimental purposes.* Rabbits that have been used previously for experimental or testing purposes with microbiological agents shall not be used as a source of kidney tissue in the production of vaccine.

(2) *Quarantine and necropsy.* Each rabbit shall be examined periodically during the quarantine period as well as at the time of necropsy under the direction of a qualified pathologist, physician or veterinarian having experience with diseases of rabbits, for the presence of signs or symptoms of ill health, particularly for evidence of tuberculosis, myxomatosis, fibromatosis, rabbit pox, and other diseases indigenous to rabbits. If there are any such signs, symptoms or other significant pathological lesions observed, tissues from that colony shall not be used in the production of vaccine.

(3) *Control vessels.* Control vessels shall be prepared, observed and tested as prescribed in §630.32(f).

(e) *Passage of virus strain in vaccine manufacture.* Virus in the final vaccine shall represent no more than five cell culture passages beyond the passage used as the seed strain for the manufacture of the vaccine used to perform the field studies (§630.60(d)), which qualified the manufacturer's vaccine strain for license.

(f) *Cell cultures in vaccine production areas.* Only the cell cultures used in the propagation of rubella virus vaccine shall be introduced into rubella virus vaccine production areas.

(g) *Test samples.* Test samples of rubella virus harvests or pools shall be withdrawn and maintained by following the procedures prescribed in §630.32(g).

[38 FR 32068, Nov. 20, 1973, as amended at 40 FR 11719, Mar. 13, 1975; 47 FR 24699, June 8, 1982; 50 FR 4138, Jan. 29, 1985; 55 FR 47876, Nov. 16, 1990]

§630.63 Reference virus.

A Reference Rubella Virus, Live, shall be obtained from the Center for Biologics Evaluation and Research as a control for correlation of virus titers.

[38 FR 32068, Nov. 20, 1973, as amended at 49 FR 23834, June 8, 1984; 55 FR 11013, Mar. 26, 1990]

§ 630.64 Potency test.

The concentration of live rubella virus shall constitute the measure of potency. The titration shall be performed in a suitable cell culture system, using either the Reference Rubella Virus, Live, or a calibrated equivalent strain as a titration control. The concentration of live rubella virus contained in the vaccine of each lot under test shall be no less than the equivalent of 1,000 $TCID_{50}$ of the reference virus per human dose.

§ 630.65 Test for safety.

(a) *Tests prior to clarification of vaccine manufactured in duck embryo cell cultures.* Prior to clarification, the following tests shall be performed on each rubella virus pool prepared in duck embryo cell cultures:

(1) *Inoculation of adult mice.* The test shall be performed in the volume and following the procedures prescribed in § 630.35(a)(1), and the virus pool is satisfactory only if equivalent test results are obtained.

(2) *Inoculation of suckling mice.* The test shall be performed in the volume and following the procedures prescribed in § 630.35(a)(2), and the virus pool is satisfactory only if equivalent test results are obtained.

(3) *Inoculation of monkey tissue cell cultures.* A rubella virus pool shall be tested for adventitious agents in the volume and following the procedures prescribed in § 630.35(a)(3), except that the virus need not be neutralized by antiserum. The rubella virus pool is satisfactory only if equivalent test results are obtained.

(4) *Inoculation of other cell cultures.* The rubella virus pool shall be tested for adventitious agents in the volume and following the procedures prescribed in § 630.35(a)(3), in rhesus or cynomolgus monkey kidney, in chick embryo, duck embryo, and in human cell cultures except that the virus need not be neutralized by antiserum. The rubella virus pool is satisfactory only if results equivalent to those in § 630.35(a)(3) are obtained.

(5) *Inoculation of embryonated chicken eggs.* A suspension of each undiluted rubella virus pool shall be tested in the volume and following the procedures prescribed in § 630.35(a)(5) except that the virus need not be neutralized by antiserum. The virus pool is satisfactory only if there is no evidence of adventitious agents.

(6) *Inoculation of embryonated duck eggs.* A suspension of each undiluted rubella virus pool shall be tested in embryonated duck eggs, following the procedures prescribed in § 630.35(a)(5), except that the virus need not be neutralized by antiserum and the volume of inoculum per egg shall not exceed 1.0 milliliter. The virus pool is satisfactory only if there is no evidence of adventitious agents.

(7) *Bacteriological tests.* In addition to the tests for sterility required pursuant to § 610.12 of this chapter, bacteriological tests shall be performed on each rubella virus pool for the presence of M. tuberculosis, both avian and human, by appropriate culture methods. The virus pool is satisfactory only if found negative for M. tuberculosis, both avian and human.

(8) *Test for avian leucosis.* The vaccine shall be tested for avian leucosis, in the volume and following the procedures prescribed in § 630.35(a)(8). The cultures are satisfactory for vaccine manufacture if found negative for avian leucosis.

(9) *Inoculation of cell cultures and embryonated eggs after neutralization of the virus with antiserum.* Each of the tests prescribed in paragraphs (a)(3), (4), (5), and (6) of this section shall be carried out also with rubella virus that has been neutralized by the addition of high titer antiserum of nonhuman, nonsimian and nonavian origin except that the volume of virus suspension of each undiluted virus pool tested shall be no less than 5 ml. The rubella antiserum shall have been prepared by using a rubella virus propagated in a cell culture system other than that used for the manufacture of the vaccine under test, and the cell culture system shall be free of extraneous agents which might elicit antibodies that could inhibit growth of any known extraneous agents which might be present in the vaccine under test. These tests may be performed either before or after clarification of the virus. The virus pool is satisfactory only if the results obtained are

equivalent to those required in those subparagraphs.

(b) [Reserved]

(c) *Tests prior to clarification of vaccine manufactured in rabbit renal cell cultures.* Prior to clarification each rubella virus pool prepared in rabbit renal cell cultures shall be tested as follows:

(1) *Inoculation of adult mice.* The test shall be performed in the volume and following the procedures prescribed in §630.35(a)(1), and the virus pool is satisfactory only if equivalent test results are obtained.

(2) *Inoculation of suckling mice.* The test shall be performed in the volume and following the procedures prescribed in §630.35(a)(2), and the virus pool is satisfactory only if equivalent test results are obtained.

(3) *Inoculation of monkey tissue cell cultures.* A rubella virus pool shall be tested for adventitious agents in the volume and following the procedures prescribed in §630.35(a)(3), except that the virus need not be neutralized by antiserum. The rubella virus pool is satisfactory only if equivalent test results are obtained.

(4) *Inoculation of other cell cultures.* The tests shall be performed in the volume and following the procedures prescribed in §630.35(a)(3) in rhesus or cynomolgus monkey kidney tissue, rabbit renal tissue and human tissue cell cultures, except that the virus need not be neutralized by antiserum. The rubella virus pool is satisfactory only if equivalent test results are obtained.

(5) *Inoculation of embryonated chicken eggs.* A suspension of each undiluted rubella virus pool shall be tested in the volume and following the procedures prescribed in §630.35(a)(5) except that the virus need not be neutralized by antiserum. The virus pool is satisfactory only if there is no evidence of adventitious agents.

(6) *Inoculation of rabbits.* A minimum of 15 ml. of each virus pool shall be tested by inoculation into at least five healthy rabbits, each weighing 1500–2500 grams. Each rabbit shall be injected intradermally in multiple sites with a total of 1.0 ml. and subcutaneously with 2.0 ml., of the virus pool, and the animals observed for at least 30 days. Each rabbit that dies after the first 24 hours of the test or is sacrificed because of illness shall be necropsied and the brain and organs removed and examined. The virus pool is satisfactory only if at least 80 percent of the rabbits remain healthy and survive the entire period and if all the rabbits used in the test fail to show lesions of any kind at the sites of inoculation and fail to show evidence of any viral infection.

(7) *Inoculation of guinea pigs.* Each of at least five guinea pigs, each weighing 350–450 grams, shall be inoculated intracerebrally with 0.1 ml. and intraperitoneally with 5 ml. of the undiluted virus pool. The animals shall be observed for at least 42 days. Each animal that dies after the first 24 hours of the test or is sacrificed because of illness, shall be necropsied. All remaining animals shall be sacrificed and necropsied at the end of the observation period. The virus pool is satisfactory only if at least 80 percent of all animals remain healthy and survive the observation period and if all the animals used in the test fail to show evidence of infection with *M. tuberculosis* or any viral infection.

(8) *Bacteriological tests.* In addition to the tests for sterility required pursuant to §610.12 of this chapter, bacteriological tests shall be performed on each rubella virus pool for the presence of *M. tuberculosis,* human, by appropriate culture methods. The rubella virus pool is satisfactory only if found negative for *M. tuberculosis,* human.

(9) *Tests for adventitious agents.* Each virus pool shall be tested for the presence of such known adventitious agents of rabbits as toxoplasma, encephalitozoon, herpes cuniculi, the vacuolating virus of rabbits, rabbit syncytial virus, myxoviruses and reoviruses. The virus pool is satisfactory only if the results of all tests show no evidence of any extraneous agent attributable to the rabbit renal tissue or the vaccine.

(10) *Inoculation of cell cultures and embryonated eggs after neutralization of the virus with antiserum.* Each of the tests prescribed in paragraphs (c)(3), (4), and (5) of this section shall be carried out also with rubella virus that has been neutralized by the addition of

high titer antiserum of nonhuman, nonsimian and nonrabbit origin following the procedures and in the volume prescribed in paragraph (a)(9) of this section. The virus pool is satisfactory only if the results obtained are equivalent to those required by that paragraph.

(d) *Clarification.* The rubella virus fluids shall be clarified by following the procedures prescribed in § 630.35(c).

[38 FR 32068, Nov. 20, 1973, as amended at 40 FR 11719, Mar. 13, 1975; 40 FR 25813, June 19, 1975]

§ 630.66 General requirements.

(a) *Final container tests.* In addition to the tests required pursuant to § 610.14 of this chapter, an immunological and virological identity test shall be performed on the final container if it was not performed on each pool or on the bulk vaccine prior to filling.

(b) *Dose.* These standards are based on an individual human immunizing dose of no less than 1,000 $TCID_{50}$ of Rubella Virus Vaccine Live, expressed in terms of the assigned titer of the Reference Rubella Virus, Live.

(c) *Labeling.* In addition to the items required by other applicable labeling provisions of this subchapter, single dose container labeling for vaccine which is not protected against photochemical deterioration shall include a statement cautioning against exposure to light.

(d) *Photochemical deterioration; protection.* Rubella Virus Vaccine Live, in multiple dose containers, shall be protected against photochemical deterioration in accordance with the procedures prescribed in § 630.36(g).

(e) *Samples; protocols; offical release.* The following shall be submitted to the Director, Center for Biologics Evaluation and Research, Food and Drug Administration, 8800 Rockville Pike, Bethesda, MD 20892:

(1) For each lot of vaccine:

(i) A protocol, which consists of a summary of the history of the manufacture of the lot, including all results of each test for which test results are requested by the Director, Center for Biologics Evaluation and Research.

(ii) A total of no less than two 25-milliliter volumes, in a frozen state (−60° C.), of preclarification bulk vaccine containing no preservative or adjuvant.

(iii) A total of no less than 30 containers of the vaccine from each filling of each bulk lot of single-dose containers. A total of no less than six 50-dose containers or ten 10-dose containers of the vaccine from each filling of each bulk lot of multiple-dose containers.

(2) In addition to the requirements of paragraph (e)(1) of this section, whenever a new production seed lot is introduced, or whenever the source of cell culture substrate must be reestablished and recertified, samples consisting of no less than 100 milliliters in 10-milliliter volumes, in a frozen state (−60° C.), of postclarification bulk vaccine containing stabilizer but no preservative or adjuvant, taken from each of 5 consecutive lots of the bulk vaccine.

(3) The product shall not be issued by the manufacturer until written notification of official release of the lot is received from the Director, Center for Biologics Evaluation and Research.

[38 FR 32068, Nov. 20, 1973, as amended at 41 FR 10430, Mar. 11, 1976; 42 FR 27582, May 31, 1977; 49 FR 23834, June 8, 1984; 50 FR 4138, Jan. 29, 1985; 51 FR 15610, Apr. 25, 1986; 55 FR 11013, Mar. 26, 1990]

Subpart H—Smallpox Vaccine

§ 630.70 Smallpox Vaccine.

(a) *Proper name and definition.* The proper name of this product shall be Smallpox Vaccine, which shall be a preparation of live vaccinia virus obtained from inoculated calves or chicken embryos.

(b) *Strains of virus.* The strain of seed virus used in the manufacture of Smallpox Vaccine shall be identified by historical records including origin and manipulation, and shall meet the sterility test requirements when tested by the procedure prescribed in § 610.12 of this chapter. The strain of seed virus and every third passage shall be tested by a rabbit scarification procedure and shown to maintain its original dermatropic properties. The test procedure is available upon request from the Director, Center for Biologics Evaluation and Research. Any new strain shall be shown not to produce a

reactivity in man exceeding that produced by the Reference Smallpox Vaccine.

[38 FR 32068, Nov. 20, 1973, as amended at 41 FR 51010, Nov. 19, 1976; 49 FR 23834, June 8, 1984; 55 FR 11013, Mar. 26, 1990]

§ 630.71 Production.

Vaccinia virus used for the manufacture of vaccine shall be obtained from vesicles on the skin of an inoculated calf or from inoculated chorioallantoic membranes of chicken embryos, as set forth below:

(a) *Virus from calves*—(1) *Quarantine.* Only calves which, prior to being placed in quarantine have reacted negatively to tuberculin, were afebrile and free of ectoparasites, and which shall have met all other applicable quarantine requirements of § 600.11(f)(2)(i) of this chapter, shall be used for vaccinia virus production. The quarantine period shall be at least 14 days. During the last 7 days of the quarantine period daily morning and afternoon rectal temperatures shall be taken and calves that do not remain afebrile during that period shall not be used for virus production.

(2) *Inoculation.* A larger area of the calf than will be used for production purposes shall be prepared in a manner comparable to that appropriate for aseptic surgery, except that the area to be inoculated must be washed free of all antiseptics that may have a deleterious effect on virus propagation. The instrument and method used for scarification must produce a uniform penetration into the epidermis but must not extend through into the corium.

(3) *Incubation.* The inoculated calf shall remain in the incubation room confined to its stall and daily morning and afternoon rectal temperatures shall be taken to determine that only the expected febrile condition occurs. If any signs of disease other than vesiculation at the inoculation site occur, the virus from that calf shall not be used for vaccine manufacture.

(4) *Harvesting.* Before harvesting, the calf shall be anesthetized and killed by exsanguination. Prior to harvesting, the inoculated area shall be thoroughly cleansed by aseptic techniques. Only the vesicular material shall be harvested.

(5) *Necropsy.* A necropsy shall be made of each production calf. The harvested material shall not be used from any animal suspected of having an infection other than vaccinia.

(b) *Virus from embryonated chicken eggs*—(1) *Eggs for production.* Embryonated chicken eggs used for propagation of vaccinia virus shall be derived from flocks found to be free of, and continuously monitored for freedom from *Salmonella pullorum,* Mycoplasma species, avian tuberculosis, fowl pox, Newcastle disease virus, Rous sarcoma virus, avian leucosis complex of viruses, and other agents pathogenic for chickens, or appropriate tests shall be performed to demonstrate freedom of the vaccine from such agents.

(2) *Harvesting.* Aseptic techniques shall be used in harvesting the chorioallantoic membranes exhibiting vesicles characteristic of vaccinia infection.

§ 630.72 Reference vaccine.

Reference Smallpox Vaccine and reconstitution fluid shall be obtained from the Center for Biologics Evaluation and Research and shall be used in all tests for determining the potency of Smallpox Vaccine.

[38 FR 32068, Nov. 20, 1973, as amended at 49 FR 23834, June 8, 1984; 55 FR 11013, Mar. 26, 1990]

§ 630.73 Potency test.

Each filling of Smallpox Vaccine shall be tested for potency by the ''pock count'' method as follows:

(a) [Reserved]

(b) *Pock counting in embryonated chicken eggs*—(1) *Dilutions* shall be made starting with no less than 0.5 ml. of the test vaccine and of the reference vaccine. The same diluent shall be used for all dilutions of both vaccines. The sample of vaccine in capillary tubes shall be obtained by pooling the contents of no less than 50 capillaries into a sterile vessel.

(2) *Inoculation of embryonated chicken eggs.* One-tenth milliliter of each dilution of test vaccine shall be inoculated onto the chorioallantoic membrane of each of at least five embryonated chicken eggs. The reference vaccine shall be tested in the same manner.

After inoculation, all eggs shall be incubated at 37°C±1°C for 48 hours.

(3) *Estimation of potency.* Only membranes from living embryos shall be removed and the number of specific lesions thereon shall be counted and recorded. The number of pock forming units in 1.0 ml. of vaccine shall be calculated from the number of lesions, the dilution factor and the volume used, to determine the titer of the undiluted vaccine. The accuracy of the titration shall be confirmed in each test by performing simultaneously the same type of titration with the reference vaccine which shall demonstrate its assigned titer.

(4) *Potency requirements*—(i) *Vaccine intended for multiple pressure administration.* Vaccine intended for multiple pressure administration shall have a titer at least equivalent to the reference vaccine.

(ii) *Vaccine intended for jet injection.* Vaccine intended for administration by jet injector shall have a number of pock forming units in one human dose at least equivalent to that contained in 0.1 ml. of the reference vaccine diluted 1:30.

(iii) *Heated liquid vaccine.* Samples of liquid vaccine from final containers taken at random shall be incubated at 35° to 37° C. for at least 18 hours, after which the heated sample shall be tested in parallel with a sample of unheated vaccine of the same lot, as prescribed in this paragraph. The vaccine is satisfactory if the heated sample retains at least one tenth of the potency of the unheated sample.

(iv) *Heated dried vaccine.* Samples of dried vaccine from final containers taken at random shall be incubated at 35° to 37° C. for 30 days, after which the heated sample shall be tested in parallel with a sample of unheated vaccine of the same lot, as prescribed in this paragraph. The vaccine is satisfactory if the heated sample retains at least one-tenth of the potency of the unheated sample.

[38 FR 32068, Nov. 20, 1973, as amended at 41 FR 51010, Nov. 19, 1976]

§ 630.74 Tests for safety.

(a) *Anaerobes.* A 10-milliliter sample representative of the homogenized viral harvest or pool of several viral harvests shall be tested for the presence of anaerobes in the following manner: Before the addition of preservatives other than glycerin, the test sample shall be inoculated into freshly heated Fluid Thioglycollate Medium using a ratio of inoculum to culture medium sufficient for optimal bacterial growth. The test vessels shall be incubated at 35° to 37° C and observed daily for 10 days for evidence of bacterial growth. If bacterial growth is observed, the organism(s) shall be identified as to genus. Within 24 to 48 hours of an indication that there may be anaerobic growth, 1.0-milliliter samples from each vessel showing growth shall be inoculated subcutaneously into each of at least three mice weighing not more than 20 grams each, and into each of three guinea pigs weighing not more than 350 grams each. The animals shall be observed daily for 6 days for signs of tetanus or presence of other anaerobes. If the animals show no signs of tetanus or presence of other anaerobes, additional groups of the same types and numbers of animals shall be injected 9 days after evidence of anaerobic bacterial growth is observed in the original planting with 1.0-milliliter samples from each test vessel showing growth. The animals shall be observed daily for 6 days for signs of tetanus or presence of other anaerobes. If any animals die within 3 days without having shown signs of tetanus or presence of other anaerobes, the test shall be repeated within 18 hours of the deaths, with 0.1-milliliter samples of the culture from which that animal was inoculated. Samples from the culture shall be injected into each of three additional test animals of the same species, and the animals shall be observed daily for 6 days. If there is any evidence of the presence of pathogenic anaerobes, the viral harvest may not be used in the manufacture of Smallpox Vaccine.

(b) [Reserved]

(c) *Coliform organisms.* A 5.0 ml. sample of bulk vaccine shall be tested for the presence of coliform organisms by the method published by the American Public Health Association, Inc., in ''Standard Methods for the Examination of Water and Wastewater'' (13th edition, 1971), section entitled ''Multiple-Tube Fermentation Technic for

Members of the Coliform Group,'' pages 662–678 and any amendments or revisions thereof, which section is hereby incorporated by reference and deemed published herein. Said publication is available at most medical and public libraries and copies of the pertinent section will be provided to any manufacturer affected by the provisions of this part upon request to the Director, Center for Biologics Evaluation and Research, or to the appropriate Information Center Officer listed in 45 CFR part 5. In addition, an official historic file of the material incorporated by reference is maintained in the Office of the Director, Center for Biologics Evaluation and Research, or available for inspection at the Office of the Federal Register, 800 North Capitol Street NW., suite 700, Washington, DC 20408. A method different than that contained in the above cited section may be used to test for the presence of coliform organisms upon a showing that it is of equal or greater sensitivity. The ratio of the volume of inoculum to the volume of culture medium shall be such as will dilute the preservative to a level that does not inhibit growth of contaminating organisms. The vaccine is satisfactory if there is no evidence of coliform organisms.

(d) *Hemolytic streptococci and coagulase-positive staphylococci.* Each of three 1.0 ml. samples of bulk vaccine shall be spread uniformly on the surface of separate blood agar plates. The plates shall be incubated for 48 hours at 35° to 37° C. The vaccine is satisfactory if there is no evidence of the presence of either hemolytic streptococci or coagulase-positive staphylococci.

(e) *Viable bacteria*—(1) *Vaccine intended for multiple pressure administration.* Samples of each lot of both bulk and final container vaccine shall be tested for viable bacteria by a procedure designed to detect both aerobic and anaerobic growth through a period of 7 days. At least three 1.0 ml. samples of bulk vaccine and three 0.2 ml. samples of vaccine derived from not less than three final containers or dilutions thereof shall be inoculated into a volume of culture medium sufficient for optimal bacterial growth. The vaccine is satisfactory if it contains no more than 200 viable organisms per ml.

(2) *Vaccine intended for jet injection.* Samples of each lot of both bulk and final container vaccine shall be tested for viable bacteria in Fluid Thioglycollate Medium prepared in accordance with §610.12(e)(1)(i) of this chapter for at least a 7-day test period. A sample of at least 10.0 ml. of bulk vaccine and 1.0 ml. from each of at least 20 final containers shall be tested. The ratio of the volume of the inoculum to the volume of culture medium shall be such as will dilute the preservative in the inoculum to a level that does not inhibit growth of contaminating micro-organisms. The vaccine is satisfactory if it contains no more than one organism per 100 doses of vaccine.

(f) *Sterile vaccine.* The tests prescribed in paragraphs (c), (d), and (e) of this section need not be performed on a lot of Smallpox Vaccine that meets the sterility requirements prescribed in §610.12 of this chapter.

[38 FR 32068, Nov. 20, 1973, as amended at 41 FR 51010, Nov. 19, 1976; 47 FR 9397, Mar. 5, 1982; 49 FR 23834, June 8, 1984; 55 FR 11013, Mar. 26, 1990]

§630.75 General requirements.

(a) *General safety.* Each lot of vaccine shall be tested for safety as prescribed in §610.11 of this chapter and shall meet the safety requirements of that section, except that for liquid Smallpox Vaccine distributed in capillaries, the test may be performed with a sample of bulk vaccine taken at the time of filling into final containers.

(b) *Preservative.* A preservative that meets the requirements of §610.15 of this chapter may be used, provided that if the preservative is phenol, its concentration shall not exceed 0.5 percent.

(c) *Labeling.* In addition to complying with all other applicable labeling provisions of this subchapter the package label shall bear the following:

(1) *Vaccine intended for jet injection.* (i) A conspicuous statement that the vaccine is intended for administration by jet injector.

(ii) A statement that the vaccine has been shown by appropriate test methods to contain not more than one organism per 100 doses or reference to an enclosed circular that contains such

information, except that such a statement is not required for vaccine which meets the sterility requirements of §610.12 of this chapter.

(2) *Vaccine intended for multiple pressure administration.* A statement that the vaccine has been shown by appropriate test methods to contain not more than 200 organisms per ml. or reference to an enclosed circular that contains such information, except that such a statement is not required for vaccine which meets the sterility requirements of §610.12 of this chapter.

(d) *Samples; protocols; official release.* (1) For each lot of vaccine the following shall be submitted to the Director, Center for Biologics Evaluation and Research, Food and Drug Administration, 8800 Rockville Pike, Bethesda, MD 20892:

(i) A protocol which consists of a summary of the history of manufacture of each filling including all results of each test for which test results are requested by the Director, Center for Biologics Evaluation and Research.

(ii) Three hundred capillaries from the first filling of a lot of liquid vaccine, and 200 capillaries from each subsequent filling.

(iii) Two 10 ml. samples of bulk liquid vaccine to be submitted along with the capillaries from the first filling and taken from the same vessel from which such capillaries were filled.

(iv) For vaccine intended for jet gun injection, a sample from each drying consisting of no less than eight 100-dose vials or eight 500-dose vials of vaccine in final labeled containers, plus sufficient diluent in final labeled containers to reconstitute the vaccine.

(v) For vaccine intended for multiple pressure administration, a sample from each drying consisting of no less than eighty 10-dose vials, ninety 25-dose vials, or eighty 100-dose vials of vaccine in final labeled containers, plus sufficient diluent in final labeled containers to reconstitute the vaccine.

(2) The product shall not be issued by the manufacturer until written notification of official release of the lot is received from the Director, Center for Biologics Evaluation and Research.

[38 FR 32068, Nov. 20, 1973, as amended at 42 FR 27582, May 31, 1977; 42 FR 56112, Oct. 21, 1977; 49 FR 23834, June 8, 1984; 51 FR 15610, Apr. 25, 1986; 55 FR 11013, Mar. 26, 1990]

PART 640—ADDITIONAL STANDARDS FOR HUMAN BLOOD AND BLOOD PRODUCTS

Subpart A—Whole Blood

Sec.

Subpart B—Red Blood Cells

Subpart C—Platelets

Subpart D—Plasma

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—Measles Immune Globulin (Human)

Subpart L—Alternative Procedures

AUTHORITY: Secs. 201, 501, 502, 503, 505, 510, 701 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, 351, 352, 353, 355, 360, 371); secs. 215, 351, 352, 353, 361 of the Public Health Service Act (42 U.S.C. 216, 262, 263, 263a, 264).

SOURCE: 38 FR 32089, Nov. 20, 1973, unless otherwise noted.

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

Subpart A—Whole Blood

§ 640.1 Whole Blood.

The proper name of this product shall be Whole Blood. Whole Blood is defined as blood collected from human donors for transfusion to human recipients.

[38 FR 32089, Nov. 20, 1973, as amended at 50 FR 4138, Jan. 29, 1985]

§ 640.2 General requirements.

(a) *Manufacturing responsibility.* All manufacturing of Whole Blood, including donor examination, blood collection, laboratory tests, labeling, storage and issue, shall be done under the supervision and control of the same licensed establishment except that the Director, Center for Biologics Evaluation and Research, may approve arrangements, upon joint request of two or more licensed establishments, which he finds are of such a nature as to assure compliance otherwise with the provisions of this subchapter.

(b) *Periodic check on sterile technique.* Where blood is collected in an open system, that is, where the blood container is entered, at least one container of such blood that upon visual examination appears normal shall be tested each month between the 18th and 24th day after collection (between the 32d and 38th day after collection when CPDA–1 solution is used as the anticoagulant), as a continuing check on technique of blood collection, as follows: The test shall be performed with a total sample of no less than 10 milliliters of blood and a total volume of fluid thioglycollate medium 10 times the volume of the sample of blood. The test sample shall be inoculated into one or more test vessels in a ratio of blood to medium of 1 to 10 for each vessel, mixed thoroughly, incubated for 7 to 9 days at a temperature of 30° to 32° C, and examined for evidence of growth of microorganisms every workday throughout the test period. On the

third, fourth, or fifth day, at least 1 milliliter of material from each test vessel shall be subcultured in additional test vessels containing the same culture medium and in such proportion as will permit significant visual inspection, mixed thoroughly, incubated for 7 to 9 days at a temperature of 30° to 32° C, and examined for evidence of growth of microorganisms every workday throughout the test period. If growth is observed in any test vessel, the test shall be repeated to rule out faulty test procedure, using another sample of blood from either, (1) the container from which the initial test sample was taken; (2) the residual cells or plasma from that blood; or (3) two different containers of blood, each 18 to 24 days old (32 to 38 days old when CPDA–1 solution is used as the anticoagulant) and each tested separately. The formula for Fluid Thioglycollate Medium shall be as prescribed in §610.12(e)(1) of this chapter. Media and design of container shall meet the requirements prescribed in §610.12(e)(2) (i) and (ii) of this chapter. In lieu of performing one test using an incubation temperature of 30° to 32° C, two tests may be performed: Each in all respects as prescribed in this paragraph, one at an incubation temperature of 18° to 22° C and one at an incubation temperature of 35° to 37° C.

(c) *Final container.* The original blood container shall be the final container and shall not be entered prior to issue for any purpose except for blood collection. Such 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.

(d) [Reserved]

(e) *Reissue of blood.* Blood that has been removed from storage controlled by a licensed establishment shall not be reissued by a licensed establishment unless the following conditions are observed:

(1) The container has a tamper-proof seal when originally issued and this seal remains unbroken;

(2) An original pilot sample is properly attached and has not been removed, except that blood lacking a pilot sample may be reissued in an emergency provided it is accompanied by instructions for sampling and for use within six hours after entering the container for sampling;

(3) The blood has been stored continuously at 1° to 6° C. and shipped between 1° and 10° C;

(4) The blood is held for observation until a significant inspection consistent with the requirements of §640.5(e) can be made.

(f) *Issue prior to determination of test results.* Notwithstanding the provisions of §610.1 of this chapter, blood may be issued by the manufacturer on the request of a physician, hospital, or other medical facility before results of all tests prescribed in §640.5, the test for hepatitis B surface antigen prescribed in §610.40(a) of this chapter, and a test for antibody to Human Immunodeficiency Virus (HIV) prescribed in §610.45(a) of this chapter have been completed, where such issue is essential to allow time for transportation to ensure arrival of the blood by the time it is needed for transfusion: *Provided,* That (1) the blood is shipped directly to such physician or medical facility, (2) the records of the manufacturer contain a full explanation of the need for such issue, and (3) the label on each container of such blood bears the information required by §606.121(h) of this chapter.

(Information collection requirements approved by the Office of Management and Budget under number 0910–0227)

[38 FR 32089, Nov. 20, 1973, as amended at 41 FR 4015, Jan. 28, 1976; 42 FR 59878, Nov. 22, 1977; 43 FR 34460, Aug. 4, 1978; 49 FR 15187, Apr. 18, 1984; 49 FR 23834, June 8, 1984; 50 FR 4138, Jan. 29, 1985; 53 FR 116, Jan. 5, 1988; 55 FR 11013, Mar. 26, 1990]

§640.3 Suitability of donor.

(a) *Method of determining.* The suitability of a donor as a source of Whole Blood shall be determined by a qualified physician or by persons under his supervision and trained in determining suitability. Such determination shall

be made on the day of collection from the donor by means of medical history, a test for hemoglobin level, and such physical examination as appears necessary to a physician who shall be present on the premises when examinations are made, except that the suitability of donors may be determined when a physician is not present on the premises, provided the establishment (1) maintains on the premises, and files with the Center for Biologics Evaluation and Research, a manual of standard procedures and methods, approved by the Director of the Center for Biologics Evaluation and Research, that shall be followed by employees who determine suitability of donors, and (2) maintains records indicating the name and qualifications of the person immediately in charge of the employees who determine the suitability of donors when a physician is not present on the premises.

(b) *Qualifications of donor; general.* Except as provided in paragraph (f), 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) A blood hemoglobin level which shall be demonstrated to be no less than 12.5 gm. of hemoglobin per 100 ml. of blood;

(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;

(2) A history of close contact within six months of donation with an individual having viral hepatitis;

(3) A history of having received within six months human blood, or any derivative of human blood which the Food and Drug Administration has advised the licensed establishment is a possible source of viral hepatitis.

(d) *Therapeutic bleedings.* Blood withdrawn in order to promote the health of a donor otherwise qualified under the provisions of this section, shall not be used as a source of Whole Blood unless the container label conspicuously indicates the donor's disease that necessitated withdrawal of blood.

(e) *Immunized donors.* Blood withdrawn from donors known to have been immunized to human blood cell antigens shall not be used for Whole Blood unless the container label conspicuously indicates such information.

(f) *Qualifications; donations within less than 8 weeks.* A person may serve as a source of Whole Blood more than once in 8 weeks only if at the time of donation the person is examined and certified by a physician to be in good health, as indicated in part in paragraph (b) of this section.

[38 FR 32089, Nov. 20, 1973, as amended at 49 FR 23834, June 8, 1984; 50 FR 4138, Jan. 29, 1985; 51 FR 15611, Apr. 25, 1986; 55 FR 11013, Mar. 26, 1990]

§ 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 clinic.* The pertinent requirements of §§ 600.10 and 600.11 of this chapter shall apply at both the licensed 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. One of the following formulae shall be used in the indicated volumes:

(1) *Anticoagulant citrate dextrose solution (ACD).*

	Solution A	Solution B
Tri-sodium citrate ($Na_3C_6H_5O_7 \cdot 2H_2O$).	22.0 gm ...	13.2 gm.
Citric acid ($C_6H_8O_7 \cdot H_2O$)	8.0 gm	4.8 gm.
Dextrose ($C_6H_{12}O_6 \cdot H_2O$)	24.5 gm ...	14.7 gm.
Water for injection (U.S.P.) to make.	1,000 ml	1,000 ml.
Volume per 100 ml. blood	15 ml	25 ml.

(2) *Anticoagulant heparin solution.*

Heparin sodium (U.S.P.)	75,000 units.
Sodium chloride injection (U.S.P.) to make	1,000 ml.
Volume per 100 ml. blood	6 ml.

A buffer to maintain stability shall be added, if necessary.

(3) *Anticoagulant citrate phosphate dextrose solution (CPD).*

Tri-sodium citrate ($Na_3C_6H_5O_7 \cdot 2H_2O$)	26.3 gm.
Citric acid ($C_6H_8O_7 \cdot H_2O$)	3.27 gm.
Dextrose ($C_6H_{12}O_6 \cdot H_2O$)	25.5 gm.
Monobasic sodium phosphate ($NaH_2PO_4 \cdot H_2O$).	2.22 gm.
Water for injection (U.S.P.) to make	1,000 ml.
Volume per 100 ml. blood	14 ml.

(4) *Anticoagulant citrate phosphate dextrose adenine solution (CPDA–1).*

Tri-sodium citrate ($Na_3C_6H_5O_7 \cdot 2H_2O$)	26.3 gm.
Citric acid ($C_6H_8O_7 \cdot H_2O$)	3.27 gm.
Dextrose ($C_6H_{12}O_6 \cdot H_2O$)	31.9 gm.
Monobasic sodium phosphate ($NaH_2PO_4 \cdot H_2O$).	2.22 gm.
Adenine ($C_5H_5N_5$)	0.275 gm.
Water for injection (U.S.P.) to make	1,000 ml.
Volume per 100 ml blood	14 ml.

(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) *Pilot samples for laboratory tests.* Pilot samples for laboratory tests shall meet the following standards:

(1) One or more pilot samples shall be provided with each unit of blood when issued or reissued except as provided in § 640.2(e)(2) and all pilot samples 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 pilot samples accompanying a unit of blood shall be collected at the time of filling the final container by the person who collects the unit of blood.

(3) All containers for all samples shall bear the donor's identification before collecting the samples.

(4) All containers for pilot samples 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) When CPDA–1 is used, pilot samples for compatibility testing shall contain blood mixed with CPDA–1.

(h) *Phlebotomy for Heparin Whole Blood.* Heparin Whole Blood shall be collected with minimal damage to and minimal manipulation of the donor's tissue, and with a single, uninterrupted, freeflowing venipuncture.

(i) *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.

[38 FR 32089, Nov. 20, 1973, as amended at 42 FR 59878, Nov. 22, 1977; 43 FR 34460, Aug. 4, 1978; 49 FR 23834, June 8, 1984; 50 FR 4138, Jan. 29, 1985; 55 FR 11013, Mar. 26, 1990]

§640.5 Testing the blood.

All laboratory tests shall be made on a pilot sample specimen of blood taken from the donor at the time of collecting the unit of blood, and these tests shall include the following:

(a) *Serological test for syphilis.* Whole Blood shall be negative to a serological test for syphilis.

(b) *Determination of blood group.* Each container of Whole Blood shall be classified as to ABO blood group. At least two blood group tests shall be made and the unit shall not be issued until grouping tests by different methods or with different lots of antiserums are in agreement. Only those Anti-A and Anti-B Blood Grouping Reagents licensed under, or that otherwise meet the requirements of, the regulations of this subchapter shall be used, and the technique used shall be that for which the serum is specifically designed to be effective.

(c) *Determination of the Rh factors.* Each container of Whole Blood shall be classified as to Rh type on the basis of tests done on the pilot 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 this test is negative, the results shall be confirmed by further testing which may include tests for the Rh_o variant (D^u) and for other Rh–Hr factors. Blood maybe labeled ''Rh Negative'' if negative to tests for the Rh_o (D) and Rh_o variant (D^u) factors. If the test using Anti-D Blood Grouping Reagent is negative, but not tested for the Rh_o variant (D^u), the label must indicate that this test was not done. Only Anti-Rh Blood Grouping Reagents licensed under, or that otherwise meet the requirements of, the regulations of this subchapter shall be used, and the technique used shall be that for which the serum is specifically designed to be effective.

(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 antibody to HIV.* Whole Blood shall be tested for antibody to HIV as prescribed in §610.45 of this chapter.

[38 FR 32089, Nov. 20, 1973, as amended at 50 FR 4138, Jan. 29, 1985; 53 FR 117, Jan. 5, 1988; 53 FR 12764, Apr. 19, 1988]

§640.6 Modifications of Whole Blood.

Upon approval by the Director, Center for Biologics Evaluation and Research, of a supplement to the product license application for Whole Blood a manufacturer may prepare Whole Blood from which the antihemophilic factor has been removed, provided the Whole Blood meets the applicable requirements of this subchapter and the following conditions are met:

(a) The antihemophilic factor shall be removed in accordance with paragraphs (a), (b), and (c) of §640.52.

(b) Although the closed system between the red blood cells and plasma shall be maintained, the red blood cells shall be maintained between 1 and 6° C at all times, including that time when the plasma is being frozen for removal of the antihemophilic factor.

(c) If containers for pilot samples are detached from the blood container during removal of the antihemophilic factor the pilot samples shall be reattached to the unit of Whole Blood Cryoprecipitate Removed as soon as the plasma is returned to the red blood

cells. The reattachment of the pilot samples shall be in a tamperproof manner that will conspicuously indicate removal and reattachment.

[38 FR 32089, Nov. 20, 1973, as amended at 49 FR 23834, June 8, 1984; 50 FR 4138, Jan. 29, 1985; 55 FR 11013, Mar. 26, 1990; 59 FR 49351, Sept. 28, 1994]

Subpart B—Red Blood Cells

§ 640.10 Red Blood Cells.

The proper name of this product shall be Red Blood Cells. The product is defined as red blood cells remaining after separating plasma from human blood.

[38 FR 32089, Nov. 20, 1973, as amended at 50 FR 4138, Jan. 29, 1985]

§ 640.11 General requirements.

(a) *Storage.* Immediately after processing, the Red Blood Cells shall be placed in storage and maintained at a temperature between 1° and 6° C.

(b) *Inspection.* The product shall be inspected immediately after separation of the plasma, periodically during storage, and at the time of issue. The product shall not be issued if there is any abnormality in color or physical appearance or if there is any indication of microbial contamination.

[38 FR 32089, Nov. 20, 1973, as amended at 41 FR 18292, May 3, 1976; 42 FR 59878, Nov. 11, 1977; 50 FR 4139, Jan. 29, 1985]

§ 640.12 Suitability of donor.

The source blood for Red Blood Cells shall be obtained from a donor who meets the criteria for donor suitability prescribed in § 640.3.

[38 FR 32089, Nov. 20, 1973, as amended at 50 FR 4139, Jan. 29, 1985]

§ 640.13 Collection of the blood.

(a) The source blood shall be collected as prescribed in § 640.4, except that paragraphs (d)(2), and (g), and (h) shall not apply.

(b) Source blood may also be derived from Whole Blood manufactured in accordance with applicable provisions of this subchapter.

[38 FR 32089, Nov. 20, 1973, as amended at 50 FR 4139, Jan. 29, 1985]

§ 640.14 Testing the blood.

Blood from which Red Blood Cells are prepared shall be tested as prescribed in §§ 610.40 and 610.45 of this chapter and § 640.5 (a), (b), and (c).

[53 FR 117, Jan. 5, 1988]

§ 640.15 Pilot samples.

Pilot samples collected in integral tubing or in separate pilot tubes shall meet the following standards:

(a) One or more pilot samples of either the original blood or of the Red Blood Cells being processed shall be provided with each unit of Red Blood Cells when issued or reissued.

(b) Before they are filled, all pilot sample tubes shall be marked or identified so as to relate them to the donor of that unit of red cells.

(c) Before the final container is filled or at the time the final product is prepared, the pilot sample tubes to accompany a unit of cells shall be attached securely to the final container in a tamper proof manner that will conspicuously indicate removal and reattachment.

(d) All pilot sample tubes 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, in each instance by the person who performs the collection or preparation.

[38 FR 32089, Nov. 20, 1973, as amended at 50 FR 4139, Jan. 29, 1985]

§ 640.16 Processing.

(a) *Separation.* Within 21 days from date of blood collection (within 35 days from date of blood collection when CPDA–1 solution is used as the anticoagulant), 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 is added for prolonged storage.

(b) *Sterile system.* All surfaces that come in contact with the red cells shall be sterile and pyrogen-free. If an open system is used, that is, where the

transfer container is not integrally attached to the blood container, and the blood container is entered after blood collection, the plasma shall be separated from the red blood cells with positive pressure maintained on the original container until completely sealed. If the method of separation involves a vented system, that is, when an airway must be inserted in the container for withdrawal of the plasma, the airway and vent shall be sterile and constructed so as to exclude microorganisms and maintain a sterile system.

(c) *Final containers.* Final containers used for Red Blood Cells shall be the original blood containers unless the method of processing requires a different container. The final container shall meet the requirements for blood containers prescribed in §640.2(c). At the time of filing, if a different container is used, it shall be marked or identified by number or other symbol so as to relate it to the donor of that unit of red cells.

[38 FR 32089, Nov. 20, 1973, as amended at 43 FR 34460, Aug. 4, 1978; 50 FR 4139, Jan. 29, 1985]

§640.17 Modifications for specific products.

Red Blood Cells Frozen: A cryophylactic substance may be added to the Red Blood Cells for extended manufacturers' storage at −65° C. or colder, provided the manufacturer submits data considered by the Director, Center for Biologics Evaluation and Research, as adequately demonstrating through in vivo cell survival and other appropriate tests that the addition of the substance, the materials used and the processing methods results in a final product that meets the required standards of safety, purity, and potency for Red Blood Cells, and that the frozen product will maintain those properties for the prescribed dating period. Section 640.11 (a) and (b) do not apply while a cryophylactic substance is present.

[38 FR 32089, Nov. 20, 1973, as amended at 41 FR 18292, May 3, 1976; 49 FR 23834, June 8, 1984; 50 FR 4139, Jan. 29, 1985; 55 FR 11013, Mar. 26, 1990]

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 license application or a supplement to the product license, 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; 55 FR 11013, Mar. 26, 1990; 59 FR 49351, Sept. 28, 1994]

§640.22 Collection of source material.

(a) Whole blood used as the source of Platelets shall be collected as prescribed in §640.4, except that paragraphs (d)(2) and (h) shall not apply.

(b) If plasmapheresis is used, the procedure for collection shall be prescribed in §§640.62, 640.64 (except paragraph (c)(3)), and 640.65.

(c) If plateletpheresis is used, the procedure for collection shall be as described in a license application or a supplement to a product license, 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.

[40 FR 4304, Jan. 29, 1975, as amended at 45 FR 27927, Apr. 25, 1980; 49 FR 23834, June 8, 1984; 50 FR 4139, Jan. 29, 1985; 55 FR 11013, Mar. 26, 1990; 59 FR 49351, Sept. 28, 1994]

§ 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 and 610.45 of this chapter and § 640.5 (a), (b), and (c).

(b) The tests shall be performed on a sample of blood collected at the time of collecting the source blood, and such sample container shall be labeled with the donor's number before the container is filled.

[40 FR 4304, Jan. 29, 1975, as amended at 50 FR 4139, Jan. 29, 1985; 53 FR 117, Jan. 5, 1988]

§ 640.24 Processing.

(a) Separation of plasma and platelets and resuspension of the platelets shall be in a closed system. Platelets shall not be pooled during processing.

(b) Immediately after collection, the whole blood or plasma shall be held in storage between 20° to 24° C, unless it must be transported from the donor clinic to the processing laboratory. During such transport, all reasonable methods shall be used to maintain the temperature as close as possible to a range between 20° and 24° C until it arrives at the processing laboratory where it shall be held between 20° and 24° C until the platelets are separated. The platelet concentrate shall be separated within 4 hours after the collection of the unit of whole blood or plasma.

(c) The time and speed of centrifugation must have been demonstrated to produce an unclumped product, without visible hemolysis, that yields a count of not less than 5.5×10^{10} platelets per unit in at least 75 percent of the units tested.

(d) The volume of original plasma used for resuspension of the platelets shall be determined by the maintenance of a pH of not less than 6.0 during the storage period. The pH shall be measured on a sample of platelets which has been stored for the maximum dating period at the selected storage temperature. One of the following storage temperatures shall be used continuously:

(1) 20° to 24° C.

(2) 1° to 6° C.

(e) Final containers used for Platelets shall be colorless and transparent to permit visual inspection of the contents; any closure shall maintain a hermetic seal and prevent contamination of the contents. The container material shall not interact with the contents, under the customary conditions of storage and use, in such a manner as to have an adverse effect upon the safety, purity, potency, or efficacy of the product. At the time of filling, the final container shall be marked or identified by number so as to relate it to the donor.

[40 FR 4304, Jan. 29, 1975, as amended at 42 FR 10983, Feb. 25, 1977; 47 FR 49021, Oct. 29, 1982; 50 FR 4139, Jan. 29, 1985]

§ 640.25 General requirements.

(a) *Storage.* Immediately after resuspension, Platelets shall be placed in storage at the selected temperature range. If stored at 20° to 24° C, a continuous gentle agitation of the platelet concentrate shall be maintained throughout the storage period. Agitation is optional if stored at a temperature between 1° and 6° C.

(b) *Quality control testing.* Each month four units prepared from different donors shall be tested at the end of the storage period as follows:

(1) Platelet count.

(2) pH of not less than 6.0 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 Act of 1967 (CLIA) (42 U.S.C. 263a) and is qualified to perform platelet counts. Such arrangements must be approved by the Director, Center for Biologics Evaluation and Research, Food and Drug Administration. Such testing shall not be considered as divided manufacturing, as described in §610.63 of this chapter, provided the following conditions are met:

(1) The results of each test are received within 10 days of the preparation of the platelet concentrate, and are maintained by the establishment licensed for Platelets so that they may be reviewed by an authorized representative of the Food and Drug Administration.

(2) The licensed Platelets manufacturer has obtained a written agreement that the testing laboratory will permit an authorized representative of the Food and Drug Administration to inspect its testing procedures and facilities during reasonable business hours.

(3) The testing laboratory will participate in any proficiency testing programs undertaken by the Center for Biologics Evaluation and Research, Food and Drug Administration.

[40 FR 4304, Jan. 29, 1975, as amended at 47 FR 49021, Oct. 29, 1982; 49 FR 23834, June 8, 1984; 50 FR 4139, Jan. 29, 1985; 55 FR 11013, Mar. 26, 1990]

§640.27 Emergency provisions.

The use of the plateletpheresis procedure to obtain a product for a specific recipient may be at variance with §§640.21(c) and 640.22(c): *Provided,* That: (a) A licensed physician has determined that the recipient must be transfused with the platelets from a specific donor, and (b) the plateletpheresis procedure is performed under the supervision of a qualified licensed physician who is aware of the health status of the donor and the physician has certified in writing that the donor's health permits plateletpheresis.

[40 FR 53544, Nov. 18, 1975]

Subpart D—Plasma

§640.30 Plasma.

(a) *Proper name and definition.* The proper name of this product shall be Plasma. The product is defined as the fluid portion of one unit of human blood intended for intravenous use which in a closed system, has been collected, stabilized against clotting, and separated from the red blood cells.

(b) *Source.* (1) Plasma shall be obtained by separating plasma from blood collected from blood donors or by plasmapheresis.

(2) Plasma may be obtained from a unit of Whole Blood collected by another licensed establishment.

[42 FR 59878, Nov. 22, 1977; 48 FR 13026, Mar. 29, 1983, as amended at 50 FR 4139, Jan. 29, 1985]

§640.31 Suitability of donors.

(a) Whole blood donors shall meet the criteria for donor suitability prescribed in §640.3.

(b) Plasmapheresis donors shall meet the criteria for donor suitability prescribed in §640.63, excluding the phrase ''other than malaria'' in paragraph (c)(9) of that section. Informed consent shall be required as prescribed in §640.61.

(c) Donors shall not be suitable if they are known to have been immunized within the past 6 months by injection with human red blood cells.

[42 FR 59878, Nov. 22, 1977]

§640.32 Collection of source material.

(a) Whole blood shall be collected, transported, and stored as prescribed in §640.4, except that paragraphs (d)(2) and (h) of that section shall not apply. When whole blood is intended for Plasma, Fresh Frozen Plasma, and Liquid Plasma, it shall be maintained at a temperature between 1° and 6° C until the plasma is removed. Whole blood intended for Platelet Rich Plasma, shall be maintained as prescribed in §640.24 until the plasma is removed. The red blood cells shall be placed in storage at

a temperature between 1° and 6° C immediately after the plasma is separated.

(b) Plasma obtained by plasmapheresis shall be collected as prescribed in §§ 640.62, 640.64 (except that paragraph (c)(3) of § 640.64 shall not apply), and § 640.65.

[42 FR 59878, Nov. 22, 1977, as amended at 45 FR 27927, Apr. 25, 1980; 50 FR 4139, Jan. 29, 1985]

§ 640.33 Testing the blood.

(a) Blood from which plasma is separated shall be tested as prescribed in §§ 610.40 and 610.45 of this chapter and § 640.5 (a), (b), and (c).

(b) Manufacturers of Plasma collected by plasmapheresis shall have testing and recordkeeping responsibilities equivalent to those prescribed in §§ 640.71 and 640.72.

[42 FR 59878, Nov. 22, 1977, as amended at 44 FR 17658, Mar. 23, 1979; 50 FR 4139, Jan. 29, 1985; 53 FR 117, Jan. 5, 1988]

§ 640.34 Processing.

(a) *Plasma.* Plasma shall be separated from the red blood cells within 26 days after phlebotomy (within 40 days after phlebotomy when CPDA–1 solution is used as the anticoagulant), and shall be stored at −18° C or colder within 6 hours after transfer to the final container, unless the product is to be stored as Liquid Plasma .

(b) *Fresh Frozen Plasma.* Fresh Frozen Plasma shall be prepared from blood collected by a single uninterrupted venipuncture with minimal damage to and minimal manipulation of the donor's tissue. The plasma shall be separated from the red blood cells, frozen solid within 6 hours after phlebotomy, and stored at −18° C or colder.

(c) *Liquid Plasma.* Liquid Plasma shall be separated from the red blood cells within 26 days after phlebotomy (within 40 days after phlebotomy when CPDA–1 solution is used as the anticoagulant) and shall be stored at a temperature of 1° to 6° C within 4 hours after filling the final container.

(d) *Platelet Rich Plasma.* Platelet Rich Plasma shall be prepared from blood collected by a single uninterrupted venipuncture with minimal damage to and manipulation of the donor's tissue. The plasma shall be separated from the red blood cells by centrifugation within 4 hours after phlebotomy. The time and speed of 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° to 24° C or between 1° and 6° C, immediately after filling the final container. A gentle and continuous agitation of the product shall be maintained throughout the storage period, if stored at a temperature of 20° to 24° C.

(e) *Modifications of Plasma.* It is possible to separate Platelets and/or Cryoprecipitated AHF from Plasma. When these components are to be separated, the plasma shall be collected as described in § 640.32 for Plasma.

(1) Platelets shall be separated as prescribed in subpart C of part 640, prior to freezing the plasma. The remaining plasma may be labeled as Fresh Frozen Plasma, if frozen solid within 6 hours after phlebotomy.

(2) Cryoprecipitated AHF shall be removed as prescribed in Subpart F of part 640. The remaining plasma may be labeled Plasma.

(3) Plasma remaining after both Platelets and Cryoprecipitated AHF have been removed may be labeled Plasma.

(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 stored in a manner that will show evidence of thawing and shall not be issued if there is any evidence of thawing of the product during storage or breakage of the container.

(3) No preservative shall be added to the final product.

[42 FR 59878, Nov. 22, 1977, as amended at 43 FR 34460, Aug. 4 1978; 48 FR 13026, Mar. 29, 1983; 50 FR 4139, Jan. 29, 1985]

Subpart E—[Reserved]

Subpart F—Cryoprecipitate

§ 640.50 Cryoprecipitated AHF.

(a) *Proper name and definition.* The proper name of this product shall be Cryoprecipitated AHF. The product is defined as a preparation of antihemophilic factor, which is obtained from a single unit of plasma collected and processed in a closed system.

(b) *Source.* The source material for Cryoprecipitated AHF shall be plasma which may be obtained by whole blood collection or by plasmapheresis.

[42 FR 21774, Apr. 29, 1977; 48 FR 13026, Mar. 29, 1983; as amended at 50 FR 4139, Jan. 29, 1985]

§ 640.51 Suitability of donors.

(a) Whole blood donors shall meet the criteria for suitability prescribed in § 640.3.

(b) Plasmaphersis 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.

(c) Donors shall not be suitable if they are known to have been immunized by injection with human red blood cells within the last 6 months.

[42 FR 21774, Apr. 29, 1977]

§ 640.52 Collection of source material.

(a) Whole blood used as a source of Cryoprecipitated AHF shall be collected as prescribed in § 640.4, except that paragraphs (d) (2), (g), and (h) of that section shall not apply. Whole blood from which both Platelets and Cryoprecipitated AHF is derived shall be maintained as required under § 640.24 until the platelets are removed.

(b) If plasmapheresis is used, the procedure for collection shall be as prescribed in §§ 640.62, 640.64 (except that paragraph (c)(3) of that section shall not apply), and 640.65.

[42 FR 21774, Apr. 29, 1977, as amended by 50 FR 4139, Jan. 29, 1985]

§ 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 and 610.45 of this chapter and § 640.5 (a), (b), and (c).

(b) The tests shall be performed on a sample of blood collected at the time of collecting the source blood, and such sample container shall be labeled with the donor's number before the container is filled.

(c) Manufacturers of Cryoprecipitated AHF obtained from plasma collected by plasmapheresis shall have testing and record-keeping responsibilities equivalent to those prescribed in §§ 640.71 and 640.72.

[42 FR 21774, Apr. 29, 1977, as amended at 42 FR 37546, July 22, 1977; 42 FR 43063, Aug. 26, 1977; 50 FR 4139, Jan. 29, 1985; 53 FR 117, Jan. 5, 1988]

§ 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 frozen solid within 6 hours after blood collection. A combination of dry ice and organic solvent may be used for freezing: *Provided,* That the procedure has been shown not to cause the solvent to penetrate the container or leach plasticizer from the container into the plasma.

(3) Immediately after separation and freezing of the plasma, the plasma shall be stored and maintained at —18° C or colder until thawing of the plasma for further processing to remove the Cryoprecipitated AHF.

(b) *Processing the final product.* (1) The Cryoprecipitated AHF shall be separated from the plasma by a procedure that has been shown to produce an average of no less than 80 units of antihemophilic factor per final container.

(2) No diluent shall be added to the product by the manufacturer prior to freezing.

(3) The final container used for Cryoprecipitated AHF shall be colorless and transparent to permit visual inspection of the contents; any closure shall maintain a hermetic seal and prevent contamination of the contents. The container material shall not interact with the contents under customary conditions of storage and use in such a manner as to have an adverse effect upon the safety, purity, potency and effectiveness of the product. At the time of filling, the final container shall be identified by a number so as to relate it to the donor.

[42 FR 21774, Apr. 29, 1977, as amended at 47 FR 15330, Apr. 9, 1982; 50 FR 4139, Jan. 29, 1985]

§ 640.55 U.S. Standard preparation.

A U.S. Standard Antihemophilic Factor (Factor VIII) preparation may be obtained from the Center for Biologics Evaluation and Research, 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.

[42 FR 21774, Apr. 29, 1977, as amended at 49 FR 23834, June 8, 1984; 50 FR 4140, Jan. 29, 1985; 55 FR 11013, Mar. 26, 1990]

§ 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 Act of 1967 (CLIA) (42 U.S.C. 263a) and is qualified to perform potency tests for antihemophilic factor. Such arrangements must be approved by the Director, Center for Biologics Evaluation and Research, Food and Drug Administration. Such testing shall not be considered as divided manufacturing, as described in §610.63 of this chapter, provided the following conditions are met:

(1) The establishment licensed for Cryoprecipitated AHF has obtained a written agreement that the testing laboratory will permit an authorized representative of the Food and Drug Administration to inspect its testing procedures and facilities during reasonable business hours.

(2) The testing laboratory will participate in any proficiency testing programs undertaken by the Center for Biologics Evaluation and Research, Food and Drug Administration.

(d) If the average potency level of antihemophilic factor in the containers tested is less than 80 units of antihemophilic factor per container, immediate corrective actions shall be taken and a record maintained of such action.

[42 FR 21774, Apr. 29, 1977, as amended at 49 FR 23834, June 8, 1984; 50 FR 4140, Jan. 29, 1985; 55 FR 11013, Mar. 26, 1990]

Subpart G—Source Plasma

§ 640.60 Source Plasma.

The proper name of the product shall be Source Plasma. The product is defined as the fluid portion of human blood collected by plasmapheresis and intended as source material for further manufacturing use. The definition excludes single donor plasma products intended for intravenous use.

[41 FR 10768, Mar. 12, 1976, as amended at 50 FR 4140, Jan. 29, 1985]

§ 640.61 Informed consent.

The written consent of a prospective donor shall be obtained after a qualified licensed physician has explained the hazards of the procedure to the prospective donor. The explanation shall include the risks of a hemolytic transfusion reaction if he is given the cells of another donor, and the hazards involved if he is hyperimmunized. The explanation shall consist of such disclosure and be made in such a manner that intelligent and informed consent

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

§ 640.62 Medical supervision.

A qualified licensed physician shall be on the premises when donor suitability is being determined, immunizations are being made, whole blood is being collected, and red blood cells are being returned to the donor.

§ 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;

(4) A normal pulse rate;

(5) A total serum protein of no less than 6.0 grams per 100 milliliters of serum;

(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;

(12) Freedom from a history of close contact within six months of donation with an individual having viral hepatitis;

(13) Freedom from a history of having received, within six months, human blood or any derivative of human blood which the Food and Drug Administration has advised the licensed establishment is a possible source of viral hepatitis, except for specific immunization performed in accordance with § 640.66 of this part.

(d) *General.* Any donor who, in the opinion of the interviewer, appears to be under the influence of any drug, alcohol, or for any reason does not appear to be providing reliable answers to medical history questions, shall not be considered a suitable donor.

(e) *Failure to return red blood cells.* Any donor who has not had the red blood cells returned from a unit of

blood collected during a plasmapheresis procedure or who has been a donor of a unit of whole blood shall not be subjected to plasmapheresis for a period of 8 weeks, unless:

(1) The donor has been examined by a qualified licensed physician and certified by the physician to be acceptable for further plasmapheresis before expiration of the 8-week period;

(2) The donor possesses an antibody that is (i) transitory, (ii) of a highly unusual or infrequent specificity, or (iii) of an unusually high titer; and

(3) The special characteristics of the antibody and the need for plasmapheresing the donor are documented.

[38 FR 32089, Nov. 20, 1973, as amended at 41 FR 10768, Mar. 12, 1976; 43 FR 9805, Mar. 10, 1978; 43 FR 12311, Mar. 24, 1978; 46 FR 57480, Nov. 24, 1981; 50 FR 4140, Jan. 29, 1985]

§ 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 Source Plasma product license.

(1) *Anticoagulant citrate dextrose solution (ACD).*

Tri-sodium citrate ($Na_3C_6H_5O_7 \cdot 2H_2O$)	22.0 grams.
Citric acid ($C_6H_8O_7 \cdot H_2O$)	8.0 grams.
Dextrose ($C_6H_{12}O_6H_2O$)	24.5 grams.
Water for injection (U.S.P.) to make	1,000 milliliters.
Volume per 100 milliliters blood	15 milliliters.

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

Tri-sodium citrate ($Na_3C_6H_5O_7 \cdot 2H_2O$)	26.3 grams.
Citric acid ($C_6H_8O \cdot H_2O$)	3.27 grams.
Dextrose ($C_6H_{12}O_6H_2O$)	25.5 grams.
Monobasic sodium phosphate ($NaH_2PO_4 \cdot H_2O$).	2.22 grams.
Water for injection (U.S.P.) to make	1,000 milliliters.
Volume per 100 milliliters blood	14 milliliters.

(3) *Anticoagulant sodium citrate solution.*

Tri-sodium citrate ($Na_3C_6H_5O_7 \cdot 2H_2O$)	40 grams.
Water for injection (U.S.P.) to make	1,000 milliliters.
Volume per 100 milliliters of blood	10 milliliters.

(d) *Donor identification.* Each unit of blood and plasma shall be so marked or identified by number or other symbol so as to relate it directly to the donor.

(e) *Prevention of contamination of the blood and plasma.* The skin of the donor at the site of phlebotomy shall be prepared thoroughly and carefully by a method that gives maximum assurance of a sterile container of blood. The blood shall be collected, the plasma separated, and the cells returned to the donor by aseptic methods in a sterile system which may be closed, or may be vented if the vent protects the blood cells and plasma against contamination.

[38 FR 32089, Nov. 20, 1973; 39 FR 13632, Apr. 16, 1974, as amended at 41 FR 10768, Mar. 12, 1976; 49 FR 23834, June 8, 1984; 50 FR 4140, Jan. 29, 1985; 55 FR 11013, Mar. 26, 1990; 59 FR 49351, Sept. 28, 1994]

§ 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 product license application.

(b) *Procedures-specific requirements.* The plasmapheresis procedure shall meet the following requirements:

(1)(i) A sample of blood shall be drawn from each donor on the day of the first medical examination or plasmapheresis, whichever comes first and at least every 4 months thereafter by a qualified licensed physician or by persons under his supervision and trained in such procedure. A serologic test for

syphilis, a total plasma or serum protein determination, and a plasma or serum protein electrophoresis or quantitative immuno-diffusion test or an equivalent test to determine immunoglobulin composition of the plasma or serum shall be performed on the sample.

(ii) A repeat donor who does not return for plasmapheresis at the time the 4-month sample is due to be collected may be plasmapheresed on the day he appears: *Provided,* That no longer than 6 months has elapsed since the last sample was collected, and the physician on the premises approves the plasmapheresis procedure and so indicates by signing the donor's record before such procedure is performed. The sample for the 4–month tests shall be collected on the day of the donor's return.

(iii) A repeat donor from whom the plasmapheresis center is unable to obtain a sample for testing as prescribed in paragraph (b)(1)(i) of this section for a total period exceeding 6 months shall be processed as a new donor.

(2)(i) The accumulated laboratory data, including tracings, if any, of the plasma or serum protein electrophoresis pattern, the calculated values of each component, and the collection records shall be reviewed by a qualified licensed physician within 21 days after the sample is drawn to determine whether or not the donor may continue in the program. The review shall be signed by the reviewing physician. If the protein composition is not within normal limits established by the testing laboratory, or if the total protein is less than 6.0 grams per 100 milliliters of samples, the donor shall be removed from the program until these values return to normal.

(ii) A donor with a reactive serologic test for syphilis shall not be plasmapheresed again until the donor's serum is tested and found to be nonreactive to a serologic test for syphilis, except as provided in paragraph (b)(2)(iii) and (iv) of this section.

(iii) A donor whose serum is determined to have a biologic false-positive reaction to a serologic test for syphilis may be plasmapheresed: *Provided,* That the donor's file identifies the serologic test for syphilis and results used to confirm the biologic false-positive reaction and indicates that the physician on the premises has determined the false-positive reaction is not the result of an underlying disorder that would disqualify the donor from participation in the plasmapheresis program. If the serologic test for syphilis is performed at a facility other than the plasmapheresis center, all applicable provisions of § 640.71 shall be met.

(iv) A donor with a reactive serologic test for syphilis may be plasmapheresed only to obtain plasma to be used for further manufacturing into control serum for the serologic test for syphilis: *Provided,* That the physician on the premises approves the donation, the donor's file contains a signed statement from a physician or clinic establishing that treatment for syphilis has been initiated and that continuance in the plasmapheresis program will not interfere with or jeopardize the treatment of the syphilitic donor.

(3) A donor identification system shall be established that positively identifies each donor and relates such donor directly to his blood and its components as well as to his accumulated records and laboratory data. Such system shall include either a photograph of each donor which shall be used on each visit to confirm the donor's identity, or some other method that provides equal or greater assurance of positively identifying the donor.

(4) The amount of whole blood, not including anticoagulant, removed from a donor during a plasmapheresis procedure or in any 48–hour 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 plasmapheresis procedure or in any 48–hour period shall not exceed 1,200 milliliters.

(5) The amount of whole blood, not including anticoagulant, removed from a donor within a seven-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 the donor during a seven-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.

[38 FR 32089, Nov. 20, 1973, as amended at 41 FR 10769, Mar. 12, 1976]

§ 640.66 Immunization of donors.

If specific immunization of a donor is to be performed, the selection and scheduling of the injection of the antigen, and the evaluation of each donor's clinical response, shall be by a qualified licensed physician or physicians. The administration of the antigen may be performed by a licensed physician or a trained person under his supervision. Any material used for immunization shall be either a product licensed under section 351 of the Public Health Service Act for such purpose or one specifically approved by the Director, Center for Biologics Evaluation and Research, Food and Drug Administration. Immunization procedures shall be on file at each plasmapheresis center where immunizations are performed.

[38 FR 32089, Nov. 20, 1973, as amended at 49 FR 23834, June 8, 1984; 55 FR 11013, Mar. 26, 1990]

§ 640.67 Laboratory tests.

(a) *Hepatitis B surface antigen.* Each unit of Source Plasma shall be nonreactive to a test for hepatitis B surface antigen as prescribed in §§ 610.40 and 610.41 of this chapter, except insofar as permitted in § 610.40(d)(1) and (d)(2) of this chapter.

(b) *Antibody to HIV.* Each unit of Source Plasma shall be negative by a test for antibody to HIV as prescribed in § 610.45 of this chapter, except as provided in § 610.45(c) of this chapter.

[53 FR 117, Jan. 5, 1988, as amended at 57 FR 10814, Mar. 31, 1992]

§ 640.68 Processing.

(a) *Sterile system.* All administration and transfer sets inserted into blood containers used for processing Source Plasma intended for manufacturing into injectable or noninjectable products and all interior surfaces of plasma containers used for processing Source Plasma intended for manufacturing into injectable products shall be sterile, pyrogen-free, nontoxic, and compatible with the contents under normal conditions of use. Only Sodium Chloride Injection USP shall be used as a red blood cell diluent. If the method of separation of the plasma intended for injectable products involves a system in which an airway must be inserted into the plasma container, the airway shall be sterile and constructed so as to exclude microorganisms and maintain a sterile system.

(b) *Final containers.* Final containers used for Source Plasma, whether integrally attached or separated from the original blood container, shall not be entered prior to issuance for any purpose except for filling with the plasma. Such containers shall be uncolored and hermetically sealed, and shall permit clear visibility of the contents. Final containers and their components shall not interact with the plasma contents under conditions of storage and use so as to alter the safety, quality, purity, or potency of the plasma and shall provide adequate protection against external factors that may cause deterioration or contamination. Prior to filling, the final container shall be marked or identified by number or other symbol which will relate it directly to the donor.

(c) *Preservative.* Source Plasma shall not contain a preservative.

[38 FR 32089, Nov. 20, 1973, as amended at 41 FR 10769, Mar. 12, 1976; 50 FR 4140, Jan. 29, 1985]

§ 640.69 General requirements.

(a) *Pooling.* Two units of Source Plasma from the same donor may be pooled if such units are collected during one plasmapheresis procedure: *Provided,* That the pooling is done by a procedure that does not introduce a risk of contamination of the red blood cells and, for plasma intended for injectable

products, gives maximum assurance of a sterile container of plasma.

(1) The pooling of plasma from two or more donors is not permitted in the manufacture of Source Plasma intended for manufacturing into injectable products.

(2) The pooling of plasma from two or more donors by the manufacturer of Source Plasma intended for manufacturing into noninjectable products is permitted: *Provided,* That the plasma from two or more donors is pooled after the plasma has been removed from the red blood cells, and after the red blood cell containers are sealed.

(b) *Storage.* Immediately after filling, plasma intended for manufacturing into injectable products shall be stored at a temperature not warmer than —20° C., except for plasma collected as provided in § 640.74. Plasma intended for manufacturing into noninjectable products may be stored at temperatures appropriate for the intended use of the final product, provided these temperatures are included in the Source Plasma license application.

(c) *Inspection.* Source Plasma intended for manufacturing into injectable products shall be inspected for evidence of thawing at the time of issuance, except that inspection of individual plasma containers need not be made if the records of continuous monitoring of the storage temperature establish that the temperature remained at —20° C or colder. If there is evidence that the storage temperature has not been maintained at —20° C or colder, the plasma may be relabeled and issued as provided in § 640.76(a).

(d) *Pilot samples.* If pilot samples are provided, they shall meet the following standards:

(1) Prior to filling, all pilot samples shall be marked or identified so as to relate them directly to the donor of that unit of plasma.

(2) All pilot samples shall be filled at the time the final product is prepared by the person who prepares the final product.

(3) All pilot samples shall be representative of the contents of the final product.

(4) All pilot samples shall be collected in a manner that does not contaminate the contents of the final container.

[38 FR 32089, Nov. 20, 1973, as amended at 41 FR 10769, Mar. 12, 1976; 41 FR 14367, Apr. 5, 1976; 50 FR 4140, Jan. 29, 1985]

§ 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.

(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 each individual unit comprising the pool.

(6) The expiration date of the plasma. If plasma intended for manufacturing into noninjectable products is pooled from two or more donors the expiration date is determined from the collection date of the oldest unit in the pool, and the pooling records shall show the collection date for each unit constituting the pool.

(7) A statement as to whether the plasma was collected from normal donors or from immunized donors. In the case of immunized donors, the label shall state the immunizing antigen.

(8) The test for hepatitis B surface antigen used for the results, or the statement ''Nonreactive for HB_s Ag by FDA required test''.

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

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

(11) The statement ''Negative by a test for antibody to HIV'', or equivalent statement.

(b) Source Plasma diverted for Source Plasma Salvaged shall be relabeled ''Source Plasma Salvaged'' as prescribed in §640.76. Immediately following the proper name of the product, the labeling shall conspicuously state as applicable, ''STORAGE TEMPERATURE EXCEEDED —20° C'' or ''SHIPPING TEMPERATURE EXCEEDED — 5° C''.

[41 FR 10770, Mar. 12, 1976, as amended at 41 FR 27034, July 1, 1976; 41 FR 35062, Aug. 19, 1976; 47 FR 30969, July 16, 1982; 50 FR 4140, Jan. 29, 1985; 50 FR 35471, Aug. 30, 1985; 53 FR 117, Jan. 5, 1988]

§ 640.71 Manufacturing responsibility.

(a) All steps in the manufacture of Source Plasma, including donor examination, blood collection, plasmapheresis, laboratory testing, labeling, storage, and issuing shall be performed by personnel of the establishment licensed to manufacture Source Plasma, except that the following tests may be performed by personnel of an establishment licensed for blood or 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 Act of 1967 (CLIA) (42 U.S.C. 263a): *Provided,* The establishment or the 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 product licenses for Source Plasma: *Provided,* That

(1) The results of such tests are maintained by the establishment licensed for Source Plasma whereby such results may be reviewed by a licensed physician as required in §640.65(b)(2) and by an authorized representative of the Food and Drug Administration.

(2) The Source Plasma manufacturer has obtained a written agreement that the testing laboratory will permit authorized representatives of the Food and Drug Administration to inspect its testing procedures and facilities during reasonable business hours.

(3) The testing laboratory will participate in any proficiency testing programs undertaken by the Center for Biologics Evaluation and Research, Food and Drug Administration.

[41 FR 10770, Mar. 12, 1976, as amended at 49 FR 23834, June 8, 1984; 50 FR 4140, Jan. 29, 1985; 53 FR 117, Jan. 5, 1988; 55 FR 11013, Mar. 26, 1990]

§ 640.72 Records.

(a) In addition to the recordkeeping requirements of this subchapter, the following records shall be maintained:

(1) Documentation compiled every 3 months establishing that the shipping temperature requirements of §600.15 of this title and §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.

(Collection of information requirements approved by the Office of Management and Budget under control number 0910–0227)

[41 FR 10770, Mar. 12, 1976, as amended at 50 FR 4140, Jan. 29, 1985; 53 FR 117, Jan. 5, 1988]

§640.73 Reporting of fatal donor reactions.

If a donor has a fatal reaction which, in any way, may be associated with plasmapheresis the Director of the Center for Biologics Evaluation and Research shall be notified by telephone as soon as possible. If the facility is located outside of the continental United States, notification by cable or telegram shall be acceptable.

[41 FR 10770, Mar. 12, 1976, as amended at 49 FR 23834, June 8, 1984; 55 FR 11013, Mar. 26, 1990]

§640.74 Modification of Source Plasma.

(a) Upon approval by the Director, Center for Biologics Evaluation and Research, Food and Drug Administration, of a supplement to the product license 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 product licensee 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.

[38 FR 32089, Nov. 20, 1973. Redesignated and amended at 41 FR 10770, Mar. 12, 1976; 49 FR 23834, June 8, 1984; 50 FR 4140, Jan. 29, 1985; 55 FR 11013, Mar. 26, 1990; 59 FR 49351, Sept. 28, 1994]

§640.76 Products stored or shipped at unacceptable temperatures.

(a) *Storage temperature.* (1) Except as provided in paragraph (a)(2) of this section, Source Plasma intended for manufacture into injectable products that

is inadvertently exposed (i.e., an unforeseen occurrence in spite of compliance with good manufacturing practice) to a storage temperature warmer than −20° C and colder than +10° C may be issued only if labeled as ''Source Plasma Salvaged.'' The label shall be revised before issuance, and appropriate records shall be maintained identifying the units involved, describing their disposition, and explaining fully the conditions that caused the inadvertent temperature exposure.

(2) Source Plasma intended for manufacture into injectable products that is exposed inadvertently (i.e., an unforeseen occurrence in spite of compliance with good manufacturing practice) to one episode of storage temperature fluctuation that is warmer than −20° C and colder than −5° C for not more than 72 hours is exempt from the labeling requirements of paragraph (a)(1) of this section, provided that the plasma has been and remains frozen solid. Appropriate records shall be maintained identifying the units involved, describing their disposition, explaining fully the conditions that caused the inadvertent temperature exposure, and documenting that the episode of temperature elevation did not exceed 72 hours, that the temperature did not rise to warmer than −5° C in storage, and that the plasma remained frozen solid throughout the period of elevated temperature. When requested, copies of the records shall be provided to the plasma derivative manufacturer.

(b) *Shipping temperature.* If Source Plasma for manufacture into injectable products is exposed inadvertently (i.e., an unforeseen occurrence in spite of compliance with good manufacturing practice) to a shipping temperature warmer than −5° C and colder than +10° C, the plasma derivative manufacturer shall label it ''Source Plasma Salvaged.'' Appropriate records shall be maintained identifying the units involved, describing their disposition, and explaining fully the conditions that caused the inadvertent temperature exposure.

(c) *Relabeling.* If Source Plasma is required to be relabeled as ''Source Plasma Salvaged'' under paragraph (a)(1) or (b) of this section, the person responsible for the relabeling shall cover the original label with either (1) a complete new label containing the appropriate information or (2) a partial label affixed to the original label and containing the appropriate new information, which covers the incorrect information regarding storage temperature.

[45 FR 80501, Dec. 5, 1980, as amended at 50 FR 4140, Jan. 29, 1985]

Subpart H—Albumin (Human)

§ 640.80 Albumin (Human).

(a) *Proper name and definition.* The proper name of the product shall be Albumin (Human). The product is defined as a sterile solution of the albumin component of human blood.

(b) *Source material.* The source material of Albumin (Human) shall be blood, plasma, serum or placentas from human donors determined at the time of donation to have been free from disease-causative agents that are not destroyed or removed by the processing method, as determined by the medical history of the donor and from such physical examination and clinical tests as may appear necessary for each donor at the time the blood was obtained. Where source material is a product for which additional standards are effective, the requirements of those additional standards shall determine the propriety of the source material for use in the production of Albumin (Human). Where no additional standards are effective with respect to source material for the production of Albumin (Human), such source material shall:

(1) Be collected by a procedure which is designed to assure the integrity and to minimize the risk of contamination of the source material. The manufacturer of Albumin (Human) shall ensure that the collection procedure shall be as described in its license.

(2) Be identified to relate it accurately to the individual donor and the dates of collection.

(3) Not contain a preservative.

(4) Be stored and transported in a manner designed to prevent contamination by microorganisms, pyrogens, or other impurities.

(c) *Additives in source material.* Source material shall not contain an additive unless it is shown that the processing method yields a final product free of

the additive to such extent that the continued safety, purity, potency, and effectiveness of the final product will not be adversely affected.

[42 FR 27582, May 31, 1977, as amended at 50 FR 4140, Jan. 29, 1985]

§ 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 either microorganisms or other deleterious matter. Preservatives to inhibit growth of microorganisms shall not be used during processing.

(d) *Storage of bulk fraction.* Bulk concentrate to be held more than 1 week prior to further processing shall be stored in clearly identified closed vessels at a temperature of —5° C or colder. Any other bulk form of the product, exclusive of the sterile bulk solution, to be held more than 1 week prior to further processing shall be stored in clearly identified closed vessels at a temperature of 5° C or colder. Any bulk fraction to be held one week or less prior to further processing shall be stored in clearly identified closed vessels at a temperature of 5° C or colder.

(e) *Heat treatment.* Heating of the final containers of Albumin (Human) shall begin within 24 hours after completion of filling. Heat treatment shall be conducted so that the solution is heated for not less than 10 or more than 11 hours at an attained temperature of 60°±0.5° C.

(f) *Stabilizer.* Either 0.16 millimole sodium acetyltryptophanate, or 0.08 millimole sodium acetyltryptophanate and 0.08 millimole sodium caprylate shall be added per gram of albumin as a stabilizer.

(g) *Incubation.* All final containers of Albumin (Human) shall be incubated at 20° to 35° C for at least 14 days following the heat treatment prescribed in paragraph (e) of this section. At the end of this incubation period, each final container shall be examined and all containers showing any indication of turbidity or microbial contamination shall not be issued. The contents of turbid final containers shall be examined microscopically and tested for sterility. If growth occurs, organisms shall be identified as to genus, and the material from such containers shall not be used for further manufacturing.

[42 FR 27582, May 31, 1977, as amended at 50 FR 4140, Jan. 29, 1985]

§ 640.82 Tests on final product.

Tests shall be performed on the final product to determine that it meets the following standards:

(a) *Protein content.* 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) *Hydrogen ion concentration.* 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 content.* The sodium content of the final product shall be 130 to 160 milliequivalents per liter.

(e) *Heme content.* The absorbance at 403 nanometers of a solution of the final product diluted to a concentration of 1 percent protein in a cell with a 1-centimeter light path shall not exceed 0.25.

(f) *Heat stability.* A final container sample of Albumin (Human) shall remain unchanged, as determined by visual inspection, after heating at 57° C for 50 hours, when compared to its control consisting of a sample, from the same lot, which has not undergone this heating.

[42 FR 27582, May 31, 1977, as amended at 49 FR 23834, June 8, 1984; 50 FR 4140, Jan. 29, 1985; 55 FR 11013, Mar. 26, 1990]

§ 640.83 General requirements.

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

(b) *Storage of bulk solution.* After all processing steps have been completed, the sterile bulk solution shall be stored in a manner that will ensure the continued sterility of the product, and at a temperature that shall not exceed the recommended storage temperature of the final product prescribed in § 610.53 of this chapter.

[42 FR 27582, May 31, 1977]

§ 640.84 Labeling.

In addition to the labeling requirements of §§ 610.60, 610.61, and 610.62 of this chapter,

(a) The container and package labels shall contain the following information:

(1) The osmotic equivalent in terms of plasma, and the sodium content in terms of a value or a range in milliequivalents per liter;

(2) 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.'';

(3) The need for additional fluids when 20 percent or 25 percent albumin is administered to a patient with marked dehydration;

(4) The protein content, expressed as a 4 percent, 5 percent, 20 percent, or 25 percent solution.

(b) The type of source material, expressed as venous plasma, placental plasma, or both, used to manufacture the final product shall appear on either the container or package label or in the package insert.

[42 FR 27582, May 31, 1977, as amended at 49 FR 2244, Jan. 19, 1984]

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 blood.

(b) *Source material.* The source material of Plasma Protein Fraction (Human) shall be blood, plasma, or serum from human donors determined at the time of donation to have been free from disease-causative agents that are not destroyed or removed by the processing method, as determined by the medical history of the donor and from such physical examination and clinical tests as may appear necessary for each donor at the time the blood was obtained. When source material is a product for which additional standards are effective, the requirements of those additional standards shall determine the propriety of the material for use in the production of Plasma Protein Fraction (Human). When no additional standards are effective with respect to source material for the production of Plasma Protein Fraction (Human), such source material shall:

(1) Be collected by a procedure which is designed to assure the integrity and to minimize the risk of contamination of the source material. The manufacturer of Plasma Protein Fraction (Human) shall ensure that the collection procedure shall be as described in its license;

(2) Be identified to relate it accurately to the individual donor and to the dates of collection;

(3) Not contain a preservative; and

(4) Be stored and transported in a manner designed to prevent contamination by microorganisms, pyrogens, or other impurities.

(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.

§ 640.91 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 coefficent 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 contimination from either microorganisms or other deleterious matter. 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 for not less than 10 or more than 11 hours at an attained temperature of 60°±0.5° C.

(f) *Stabilizer.* Either 0.16 millimole sodium acetyltryptophanate, or 0.08 millimole sodium acetyltryptophanate and 0.08 millimole sodium caprylate shall be added per gram of protein as a stabilizer.

(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.

§ 640.92 Tests on final product.

Tests shall be performed on the final product to determine that it meets the following standards:

(a) *Protein content.* The final product shall be a 5.0±0.3 percent solution of protein.

(b) *Protein composition.* The total protein in the final product shall consist of at least 83 percent albumin, and no more than 17 percent globulins. No more than 1 percent of the total protein shall be gamma globulin. The protein composition shall be determined by a method that has been approved for each manufacturer by the Director, Center for Biologics Evaluation and Research, Food and Drug Administration.

(c) *Hydrogen ion concentration.* The pH shall be 7.0±0.3 when measured in a solution of the final product diluted to a concentration of 1 percent protein with 0.15 molar sodium chloride.

(d) *Sodium content.* The sodium content of the final product shall be 130 to 160 milliequivalents per liter.

(e) *Potassium content.* The potassium content of the final product shall not exceed 2 milliequivalents per liter.

(f) *Heat stability.* A final container sample of Plasma Protein Fraction (Human) shall remain unchanged, as determined by visual inspection, after heating at 57° C for 50 hours, when compared to its control consisting of a sample, from the same lot, which has not undergone this heating.

[42 FR 27583, May 31, 1977, as amended at 49 FR 23834, June 8, 1984; 55 FR 11013, Mar. 26, 1990]

§ 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 content in terms of a value or a range in milliequivalents per liter.

(b) The cautionary statement placed in a prominent position on the label, ''Do Not Use if Turbid. Do Not Begin Administration More than 4 Hours After the Container Has Been Entered.''

[42 FR 27583, May 31, 1977, as amended at 49 FR 2244, Jan. 19, 1984]

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 blood.

(b) *Source material.* The source of Immune Globulin (Human) shall be blood, plasma or serum from human donors determined at the time of donation to have been free of causative agents of diseases that are not destroyed or removed by the processing methods, as determined by the donor's history and from such physical examination and clinical tests as appear necessary for each donor at the time the blood was obtained. The source blood, plasma or serum shall not contain a preservative and shall be stored in a manner that will prevent contamination by microorganisms, pyrogens or other impurities.

(c) *Additives in source material.* Source blood, plasma or serum shall contain no additives other than citrate or acid citrate dextrose anticoagulant solution, unless it is shown that the processing method yields a product free of the additive to such an extent that the safety, purity and potency of the product will not be affected adversely.

[38 FR 32089, Nov. 20, 1973, as amended at 50 FR 4140, Jan. 29, 1985]

§ 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) *Hydrogen ion concentration.* The pH of final container material shall be 6.8±0.4 when measured in a solution diluted to 1 percent protein with 0.15 molar sodium chloride.

(c) *Turbidity.* The product shall be free of turbidity as determined by visual inspection of final containers.

(d) *Date of manufacture.* The date of manufacture is the date of initiating the last valid measles or poliomyelitis antibody test (§ 640.104(b) (2) and (3)) whichever date is earlier.

(e) *Labeling.* In addition to complying with all applicable labeling required in this subchapter, labeling shall indicate that:

(1) There is no prescribed potency for viral hepatitis antibodies.

(2) The product is not recommended for intravenous administration.

(3) The lot is or is not suitable for use with Measles Virus Vaccine Live.

(4) The lot is or is not recommended for poliomyelitis.

(f) *Samples and protocols.* For each lot of Immune Globulin (Human) the following material shall be submitted to the Director, Center for Biologics Evaluation and Research, Food and Drug Administration, 8800 Rockville Pike, Bethesda, MD 20892:

(1) A 50 ml. sample of the final product.

(2) All protocols relating to the history of each lot and all results of all tests prescribed in these additional standards.

[38 FR 32089, Nov. 20, 1973; 48 FR 13026, Mar. 29, 1983, as amended at 49 FR 23834, June 8, 1984; 50 FR 4140, Jan. 29, 1985; 51 FR 15611, Apr. 25, 1986; 55 FR 11013, Mar. 26, 1990]

§ 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 30° to 32° C. for more than 72 hours.

[38 FR 32089, Nov. 20, 1973, as amended at 50 FR 4140, Jan. 29, 1985]

§ 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 90 percent of the globulin shall have an electrophoretic mobility not faster than -2.8×10^{-5} centimeters^2 per volt per second, when measured at a 1 percent protein concentration in sodium diethylbarbiturate buffer at pH 8.6 and 0.1 ionic strength.

§ 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 of no less than 0.50 times the level of the Reference Immune Serum Globulin, except that when recommended for use with Measles Virus Vaccine Live, the measles antibody level shall be as prescribed in § 640.114.

(3) A poliomyelitis neutralizing antibody level of no less than 1.0 for Type 1, 1.0 for Type 2, and 2.5 for Type 3, times the antibody level of the Reference Immune Serum Globulin.

(c) *Reference materials.* The following reference materials shall be obtained from the Center for Biologics Evaluation and Research:

(1) Reference Immune Serum Globulin for correlation of measles antibody titers.

(2) Reference Immune Serum Globulin for correlation of poliomyelitis antibody titers, Types 1, 2, and 3.

[38 FR 32089, Nov. 20, 1973, as amended at 39 FR 9661, Mar. 13, 1974; 49 FR 23834, June 8, 1984; 50 FR 4140, Jan. 29, 1985; 55 FR 11013, Mar. 26, 1990]

Subpart K—Measles Immune Globulin (Human)

§ 640.110 Measles Immune Globulin (Human).

(a) *Proper name and definition.* The proper name of the product shall be Measles Immune Globulin (Human). It shall consist of a sterile solution of 10 to 18 percent globulin derived from human blood, having the same measles antibody level as the Reference Measles Immune Globulin. Measles Immune Globulin shall be made from a sterile 16.5 ±1.5 percent solution of human globulin.

(b) *Source material.* The source of Measles Immune Globulin (Human) shall be blood, plasma or serum from human donors determined at the time of donation to have been free of causative agents of diseases that are not destroyed or removed by the processing method, as determined by the donor's history and from such physical examination and clinical tests as appear necessary for each donor at the time the blood was obtained. The source blood, plasma or serum shall not contain a preservative and shall be stored in a manner that will prevent contamination by microorganisms, pyrogens or other impurities.

(c) *Additives in source material.* Source blood, plasma or serum shall contain no additives other than citrate or acid citrate dextrose anticoagulant solution, unless it is shown that the processing method yields a product free of the additive to such an extent that the safety, purity and potency of the product will not be affected adversely.

[38 FR 32089, Nov. 20, 1973, as amended at 39 FR 9661, Mar. 13, 1974]

§ 640.111 General requirements.

(a) *Heat stability test.* Approximately 2 ml of final container material of each lot shall not show any visible sign of gelation after heating in a 12 × 75 mm. stoppered glass tube at 57° C. for four hours.

(b) *Hydrogen ion concentration.* 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 antibody test as required in § 640.114.

(e)—(f) [Reserved]

(g) *Samples and protocols.* For each lot of globulin, the following materials shall be submitted to the Director, Center for Biologics Evaluation and Research, Food and Drug Administration, 8800 Rockville Pike, Bethesda, MD 20892.

(1) 30 ml of final product.

(2) All protocols relating to the history of the manufacture of each lot and all results of all tests prescribed in these additional standards.

[38 FR 32089, Nov. 20, 1973, as amended at 49 FR 23834, June 8, 1984; 51 FR 15611, Apr. 25, 1986; 55 FR 11013, Mar. 26, 1990]

§ 640.112 Manufacture of Measles Immune Globulin (Human).

(a) *Processing method.* The globulin shall be prepared by a processing method that (1) has been shown to be capable of concentrating tenfold from source material at least two different antibodies, (2) does not affect the integrity of the globulins and is capable of consistently yielding a product which is safe for subcutaneous and intramuscular injections and (3) will not transmit viral hepatitis.

(b) *Reference materials.* The following reference material shall be obtained from the Center for Biologics Evaluation and Research: Reference Measles Immune Globulin for correlation of measles antibody titers with globulin products.

(c) *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.

(d) *Bulk storage.* The globulin fraction may be stored in bulk prior to further processing provided it is stored in well-marked hermetically closed vessels. Purified globulin as either a liquid concentrate or a solid and containing alcohol or more than 5 percent moisture shall be stored at a temperature not to exceed −10° C. Purified globulin as a solid free from alcohol and containing less than 5 percent moisture, shall be stored at temperatures not to exceed 0° C.

(e) *Determination of the lot.* Each lot of Measles Immune Globulin (Human) shall represent a pooling of material from not less than 1,000 donors.

(f) *Sterilization and dilution.* The product shall be prepared initially as a 16.5 percent solution and this preparation shall be sterilized promptly after solution. After sterilization the product shall not be exposed to temperatures above 45° C. for more than a total of 72 hours. Dilution of this sterile globulin

solution shall be made only to adjust the required measles antibody level.

[38 FR 32089, Nov. 20, 1973, as amended at 39 FR 9661, Mar. 13, 1974; 49 FR 23834, June 8, 1984; 55 FR 11013, Mar. 26, 1990]

§ 640.113 The final product.

(a) *Final solution.* The final product shall be a 10 to 18 percent solution of globulin containing 0.3 molar glycine and a preservative.

(b) *Protein composition.* No less than 90 percent of the globulin shall have an electrophoretic mobility not faster than -2.8×10^{-5} centimeters^2 per volt per second, when measured at a 1 percent protein concentration in sodium diethylbarbiturate at pH 8.6 and 0.1 ionic strength.

§ 640.114 Potency.

Antibody levels and tests. Each lot of final product shall contain no less than the minimum levels of antibodies for diphtheria and measles as follows:

(a) The product shall contain no less than 2 units of diphtheria antitoxin per ml, adjusted for dilution from the 16.5 percent solution.

(b) Each lot of final product shall contain the same measles antibody level as the Reference Measles Immune Globulin. The measles antibody potency shall be determined by simultaneous determinations of the neutralizing antibody titers of the globulin on tests and of a reference preparation against 100 $TCID_{50}$ (50–500 $TCID_{50}$ when based upon a single test) of measles virus in a tissue culture system. The potency test shall also include a determination of virus titer and controls for globulin toxicity and cell culture viability. Twofold serial dilutions of the globulin under test and of the reference preparation shall be employed in this determination. In applying these requirements a plus or minus variation of one twofold dilution is acceptable.

[38 FR 32089, Nov. 20, 1973, as amended at 39 FR 9661, Mar. 13, 1974]

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 should ordinarily be made in writing. 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 followed by written requests and written approvals. Approval of a request for an exception or alternative must be obtained from the Director prior to the distribution of any affected blood, blood component, or blood product.

(b) FDA will publish a list of approved alternative procedures and exceptions periodically in the FEDERAL REGISTER.

[55 FR 10423, Mar. 21, 1990]

PART 650—ADDITIONAL STANDARDS FOR DIAGNOSTIC SUBSTANCES FOR DERMAL TESTS

Subpart A—Diphtheria Toxin for Schick Test

Sec.

Subpart B—Tuberculin

AUTHORITY: Secs. 201, 501, 502, 503, 505, 510, 701 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, 351, 352, 353, 355, 360, 371); secs. 215, 351, 352, 353, 361 of the Public Health Service Act (42 U.S.C. 216, 262, 263, 263a, 264).

SOURCE: 38 FR 32097, 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—Diphtheria Toxin for Schick Test

§ 650.1 Diphtheria Toxin for Schick Test.

The proper name of this product shall be Diphtheria Toxin for Schick Test, which shall be a preparation of a diphtheria toxin obtained from the growth of *Corynebacterium diphtheriae.*

§ 650.2 U.S. Standard preparation.

The U.S. Standard Diphtheria Toxin for Schick Test shall be used to determine the Schick test dose of the product. The Schick test dose of the standard is that amount of the standard that, when mixed with 0.001 unit of the U.S. Standard Diphtheria Antitoxin and injected intradermally in a guinea pig, will induce an erythematous reaction of 10 mm. in diameter.

§ 650.3 Manufacture of Diphtheria Toxin for Schick Test.

(a) *Propagation of bacteria.* The culture medium for propagation of the *Corynebacterium diphtheriae* for preparation of the parent toxin shall not contain ingredients known to be capable of producing allergenic effects in human subjects.

(b) *The parent toxin.* Diphtheria Toxin for Schick Test shall be prepared from a parent toxin which has been demonstrated to be stable and which contains no less than 400 minimum lethal doses per milliliter or 400,000 minimum reaction doses per milliliter. A minimum lethal dose is the smallest amount of toxin that will kill a guinea pig weighing approximately 250 gm. on the fourth day after its subcutaneous injection. A minimum reaction dose is that amount of toxin which when injected intradermally into a guinea pig induces an erythematous reaction 10 mm. in diameter.

§ 650.4 Potency test.

The dermal reactivity of each lot of the product shall be determined from the results of simultaneous guinea pig intradermal potency tests of the product under test and of the standard. The test shall be performed as follows:

(a) *Guinea pigs.* At least four healthy female guinea pigs shall be used, all of the same strain and each of a size that will permit a random distribution of eight intradermal injections. The hair shall be removed from the back and both sides of each guinea pig without producing abrasions of the skin. The denuded skin of each animal shall be sectioned into four equal areas at right angles to the vertebral column to provide two injection sites in each of the four areas, one on each side of the vertebra. The test is not valid if the guinea pigs do not show a graded response to the graded dilutions of the Schick test dose of the standard toxin.

(b) *Preparation of the test doses.* Four dilutions, two of the product under test and two of the U.S. Standard Diphtheria Toxin for Schick Test, shall be prepared in sterile buffered saline pH 7.4 containing 0.2 percent gelatin. The low and high dilutions of the standard shall be those amounts of a Schick test dose of the standard which in a dose of 0.1 ml. are capable of eliciting graded erythematous dermal reactions between 10 mm. and 20 mm. in diameter. The low and high dilutions of the Schick test dose of the toxin under test shall be the same as those of the standard toxin and estimated to have the same dermal reactivity.

(c) *Inoculation.* The low and high dilutions of the product (chart designation P_L and P_H) and the low and high dilutions of the standard (chart designations S_L and S_H) shall be injected intradermally in a volume of 0.1 ml. into each of the four guinea pigs according to either the following scheme, or in another scheme, provided it will permit comparable randomization of injection sites:

Area	Guinea Pig Number							
	1		2		3		4	
	Left	Right	Left	Right	Left	Right	Left	Right
A	S_L	S_L	S_H	S_H	P_L	P_L	P_H	P_H
B	S_H	S_H	S_L	S_L	P_H	P_H	P_L	P_L

Area	Guinea Pig Number							
	1		2		3		4	
	Left	Right	Left	Right	Left	Right	Left	Right
C	P_L	P_L	P_H	P_H	S_L	S_L	S_H	S_H
D	P_H	P_H	P_L	P_L	S_H	S_H	S_L	S_L

(d) *Calculation of test results.* Between 40 and 66 hours following injection, a diameter of the reaction for each injection site shall be calculated by averaging two diameters of the reaction measured at right angles to each other. The average reaction for each dilution for each animal shall be determined, then the average diameters of the reactions of all of the guinea pigs for each dilution shall be calculated. The ratios of the reactions are determined by dividing the average diameter of the low dilution of the product under test by the average diameter of the low dilution of the standard and by dividing the average diameter of the high dilution of the product by the average diameter of the high dilution of the standard.

(e) *Potency requirement.* The potency of the product under test is satisfactory if each calculated ratio of the reactions of the product under test and of the standard is 1.0. The potency of the lot under test is considered to be equal to that of the standard if the ratios are not lower than 0.77 or higher than 1.30, provided that in a single test the ratios are substantially the same.

§650.5 Stability test.

A sample of each lot of the product shall be held at 37° C for not less than 24 hours and then tested for potency as prescribed in §650.4. The stability of the product is satisfactory if test results of the sample meet the potency requirement prescribed in §650.4(e).

§650.6 Samples; protocols; official release.

For each lot of the product, the following material shall be submitted to the Director, Center for Biologics Evaluation and Research:

(a) A protocol which consists of a summary of the history of manufacture of each lot including all results of all tests for which test results are requested by the Director, Center for Biologics Evaluation and Research.

(b) A sample of no less than 20 milliliters of the product.

(c) The product shall not be issued by the manufacturer until written notification of official release of the lot is received from the Director, Center for Biologics Evaluation and Research.

[38 FR 32097, Nov. 20, 1973, as amended at 42 FR 27584, May 31, 1977; 49 FR 23834, June 8, 1984; 55 FR 11013, Mar. 26, 1990]

Subpart B—Tuberculin

§650.10 Tuberculin.

The proper name of this product shall be Tuberculin, which shall be a preparation derived from *Mycobacterium tuberculosis* or *M. Bovis.*

§650.11 General requirements.

(a) *General safety.* Each lot of Tuberculin shall be tested for safety as prescribed in §610.11 of this chapter, except that the sample of tuberculin from multiple puncture devices shall be obtained by removing the tuberculin in a manner that will permit the injection of material from at least five devices into each of two guinea pigs and from at least two devices into each of two mice.

(b) *Labeling.* In addition to complying with all other applicable labeling provisions of this subchapter, the package label shall state the following:

(1) For Tuberculin for Mantoux testing, the number of U.S. units (TU) per dose.

(2) For Tuberculin for multiple puncture testing, a statement indicating that the activity per test is comparable to a stated number of U.S. units (TU) administered by the Mantoux method.

(3) The applicable type of Tuberculin placed immediately following and of no less prominence than the proper name, as follows:

(i) ''Old,'' or

(ii) ''Purified Protein Derivative'' or ''PPD.''

(c) *Samples; protocols; official release.* For each lot of Tuberculin the following shall be submitted to the Director, Center for Biologics Evaluation and Research, Food and Drug Administration, 8800 Rockville Pike, Bethesda, MD 20892:

(1) A protocol which consists of a summary of the history of manufacture of each lot including all results of each test for which test results are requested by the Director, Center for Biologics Evaluation and Research.

(2) Tuberculin distributed on a multiple puncture device, as follows:

(i) A total of no less than 50 devices.

(ii) A total of no less than 6 milliliters of bulk tuberculin.

(3) A total of no less than 20 ml. of liquid tuberculin.

(4) Sufficient dried tuberculin in final containers so that upon reconstitution as recommended in labeling it will yield at least 20 milliliters.

(5) The product shall not be issued by the manufacturer until written notification of official release of the lot is received from the Director, Center for Biologics Evaluation and Research.

[38 FR 32097, Nov. 20, 1973, as amended at 39 FR 9661, Mar. 13, 1974; 42 FR 27584, May 31, 1977; 42 FR 54546, Oct. 7, 1977; 49 FR 23834, June 8, 1984; 51 FR 15611, Apr. 25, 1986; 55 FR 11013, Mar. 26, 1990]

§ 650.12 U.S. Standard preparations.

(a) The U.S. Standard Tuberculin, Old, shall be used for determining the potency of nonfractionated tuberculins, as prescribed in § 650.14. One U.S. Tuberculin unit is 0.1 ml. of a 1:10,000 dilution of this standard.

(b) The U.S. Standard Tuberculin, Purified Protein Derivative, shall be used in determining the potency of tuberculins made from protein fractions, as prescribed in § 650.14. One U.S. Tuberculin unit is 0.1 ml. of a 1:5,000 dilution of this standard.

§ 650.13 Production.

(a) *Propagation of mycobacteria.* The medium used for production of mycobacteria shall not contain ingredients known to be capable of producing allergenic effects in human subjects.

(b) *Tests for viable mycobacteria.* The culture filtrate from each strain in its most concentrated form shall be shown to be free of viable mycobacteria by the following tests:

(1) *Animal test.* A 1.0 ml. sample of the filtrate shall be injected intraperitoneally into each of at least three healthy guinea pigs weighing between 300 and 400 gm. At least two-thirds of the animals must survive an observation period of at least 6 weeks and must show a normal weight gain. After the observation period the animals shall be necropsied and examined for signs indicative of tuberculosis except that animals that die during the observation period shall be necropsied and examined as soon as feasible after death. The filtrate is satisfactory for Tuberculin manufacture if none of the animals in the test show evidence of tuberculosis infection.

(2) *Culture test.* A 2.0 ml. sample of the filtrate shall be inoculated onto Lowenstein-Jensen's egg medium or other media demonstrated to be equally capable of supporting growth. A control test on the culture medium shall be conducted simultaneously with the sample under test and shall be shown to be capable of supporting the growth of small numbers of the production strain(s). All the test vessels shall be incubated at a suitable temperature for a period of 6 weeks under conditions that will prevent drying of the medium, after which the cultures shall be examined for evidence of mycobacterial colonies. The filtrate is satisfactory for Tuberculin manufacture if the test shows no evidence of mycobacteria.

(c) *Chemical characterization.* Each batch of powdered tuberculin material shall be chemically characterized, including protein, carbohydrate, lipid, and nucleic acid content to assess consistency of production.

[38 FR 32097, Nov. 20, 1973, as amended at 44 FR 40289, July 10, 1979]

§ 650.14 Potency testing in animals.

The potency of each lot of Tuberculin shall be estimated from a comparison of the responses obtained by the intradermal injection into sensitized guinea pigs weighing over 500 gm. of a sample of the lot under test and of the

appropriate standard preparation. The U.S. Standard Tuberculin, Old, shall be used in determining the potency of tuberculins made from the concentrated filtrate of the soluble products of the growth of the mycobacteria. The U.S. Standard Tuberculin, Purified Protein Derivative, shall be used in determining the potency of tuberculins made from protein fraction of the soluble products of the growth of the mycobacteria. The test shall be performed as follows:

(a) *Sensitization of test animals.* At least four white guinea pigs shall be sensitized with *M. tuberculosis* or *M. bovis.* The degree of sensitivity shall be such that an intradermal injection of one U.S. unit of the appropriate standard preparation will produce in each test animal an erythematous reaction approximately 100 mm^2 within 18–24 hours.

(b) *Test Procedure.* The hair shall be removed from both sides of the sensitized test animals without producing abrasions of the skin. Dilutions of the standard containing 0.5, 1, 2, and 4 U.S. units in the test dose of 0.1 ml. and four comparable levels of activity of the lot under test shall be injected intradermally into opposite and parallel sites of each animal. Only three dilutions need be used when the initial concentration of the lot under test does not contain four units in 0.1 ml. Within 18–24 hours following injection, measurements of the greater and lesser diameters of erythema measured to the closest millimeter shall be made at each site. The mean value of the product of the diameters for each dilution shall be calculated. The number of U.S. units in the lot under test shall be estimated from its relationship to the reactivity of the appropriate standard preparation using results from all valid tests performed.

(c) *Potency.* The potency of the lot is satisfactory if the results are within ± 20 percent of the U.S. units claimed by the manufacturer in the license application and the product labeling.

[38 FR 32097, Nov. 20, 1973, as amended at 42 FR 38567, July 29, 1977; 44 FR 40289, July 10, 1979]

§ 650.15 Potency testing in humans.

(a) The sensitivity of each batch of tuberculin material for use on multiple puncture devices for screening purposes shall be demonstrated to be sufficient to elicit an induration of 2 millimeters or more at one or more of the puncture sites or at a coalescence of more than one site in at least 95 percent of at least 50 persons who are known to have had bacteriologically confirmed tuberculosis and who are tuberculin positive as demonstrated by a simultaneous Mantoux test that elicits an induration of 5 millimeters or more when tested with 5 TU of Tuberculin, Purified Protein Derivative.

(b) The product effectiveness of each batch of tuberculin material for use by the Mantoux method shall include comparison of the product with the standard by means of (1) dose response curves, and (2) distribution of reaction sizes in persons presumed to be uninfected with *Mycobacterium tuberculosis* or other mycobacteria, in persons known to be infected with *Mycobacterium tuberculosis,* and in persons presumed to be infected with other mycobacteria.

(c) All trials in paragraphs (a) and (b) of this section shall be performed in a randomized double-blind fashion whenever possible and all reactions in each test subject shall be read by more than one competent and responsible individual.

[44 FR 40289, July 10, 1979]

PART 660—ADDITIONAL STANDARDS FOR DIAGNOSTIC SUBSTANCES FOR LABORATORY TESTS

Subpart A—Antibody to Hepatitis B Surface Antigen

Sec.

AUTHORITY: Secs. 201, 501, 502, 503, 505, 510, 701 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, 351, 352, 353, 355, 360, 371); secs. 215, 351, 352, 353, 361 of the Public Health Service Act (42 U.S.C. 216, 262, 263, 263a, 264).

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—Antibody to Hepatitis B Surface Antigen

§ 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]

§ 660.2 General requirements.

(a) *Processing.* The processing method shall be one that has been shown to consistently yield a specific and potent final product free of properties which would adversely affect the test results when the product is tested by the methods recommended by the manufacturer in the package enclosure.

(b) *Ancillary reagents and materials.* All ancillary reagents and materials supplied in the package with the product shall meet generally accepted standards of purity and quality and shall be effectively segregated and otherwise manufactured in a manner (such as heating at 60° C. for 10 hours) that will reduce the risk of contaminating the product and other biological products. Ancillary reagents and materials accompanying the product which are used in the performance of the test as described by the manufacturer's recommended test procedures shall have been shown not to adversely affect the product within the prescribed dating period.

(c) *Labeling.* In addition to the items required by other applicable labeling provisions of this subchapter, the following shall also be included:

(1) Indication of the source of the product immediately following the

proper name on both the final container and package label, e.g., human, guinea pig.

(2) Name of the test method(s) recommended for 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).

(3) A warning on the package label and on the final container label if capable of bearing a full label (see § 610.60(a) of this chapter) indicating that the product and antigen if supplied, shall be handled as if capable of transmitting hepatitis.

(4) If the product is dried, the final container label shall indicate ''Reconstitution date: ————————'' and a statement indicating the period within which the product may be used after reconstitution.

(5) The package shall include a package enclosure providing (i) adequate instructions for use, (ii) a description of all recommended test methods, and (iii) warnings as to possible hazards, including hepatitis, in handling the product and any ancillary reagents and materials accompanying the product.

(d) *Final container.* A final container shall be sufficiently transparent to permit visual inspection of the contents for presence of particulate matter and increased turbidity. The effectiveness of the contents of a final container shall be maintained throughout its dating period.

(e) *Date of manufacture.* The date of manufacture of Antibody to Hepatitis B surface Antigen that has been iodinated with radioactive iodine (^{125}I) shall be the day of labeling the antibody with the radionuclide.

(f) *Retention samples.* Each manufacturer shall retain representative samples of the product in accordance with § 600.13 of this chapter except for that which has been iodinated with radioactive iodine. Retention samples of Antibody to Hepatitis B Surface Antigen iodinated with ^{125}I shall consist of a minimum of two complete finished packages of each lot of the diagnostic test kit and shall be retained for a period of at least 90 days from the date of manufacture.

[38 FR 32098, Nov. 20, 1973, as amended at 40 FR 29711, July 15, 1975; 46 FR 36134, July 14, 1981; 49 FR 1684, Jan. 13, 1984]

§ 660.3 Reference panel.

A Reference Hepatitis B Surface Antigen Panel shall be obtained from the Center for Biologics Evaluation and Research and shall be used for determining the potency and specificity of Antibody to Hepatitis B Surface Antigen.

[40 FR 29711, July 15, 1975, as amended at 49 FR 23834, June 8, 1984; 55 FR 11013, Mar. 26, 1990]

§ 660.4 Potency test.

To be satisfactory for release, each filling of Antibody to Hepatitis B Surface Antigen shall be tested against the Reference Hepatitis B Surface Antigen Panel and shall be sufficiently potent to detect the antigen in the appropriate sera of the reference panel by all test methods recommended by the manufacturer in the package insert.

[40 FR 29711, July 15, 1975]

§ 660.5 Specificity.

Each filling of the product shall be specific for antibody to hepatitis B surface antigen, as determined by specificity tests found acceptable by the Director, Center for Biologics Evaluation and Research.

[40 FR 29712, July 15, 1975, as amended at 49 FR 23834, June 8, 1984; 55 FR 11013, Mar. 26, 1990]

§ 660.6 Samples; protocols; official release.

(a) *Samples.* (1) For the purposes of this section, a sample of product not iodinated with ^{125} I 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 ^{125} I 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 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 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.

(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) *Offical 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 samples from 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, as applicable, manufactured after licensure of the product, 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 required 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.

[48 FR 20407, May 6, 1983, as amended at 49 FR 23834, June 8, 1984; 51 FR 15611, Apr. 25, 1986; 55 FR 11013 and 11014, Mar. 26, 1990]

Subpart B—[Reserved]

Subpart C—Blood Grouping Reagent

SOURCE: 53 FR 12764, Apr. 19, 1988, unless otherwise noted.

§ 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 prepared by a method demonstrated to yield consistently a sterile product and 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.

§ 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 sterile filtered shall constitute a lot.

(3) A lot may be subdivided into clean, sterile vessels. Each subdivision shall constitute a sublot. 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.

(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 product license application.

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

(Information collection requirements approved by the Office of Management and Budget under control number 0910–0209)

§ 660.22 Potency requirements with reference preparations.

(a) *Potency requirements.* Products for which reference Blood Grouping Reagents are available shall have a potency titer value at least equal to that of the reference preparation.

(b) *Reference preparations.* Reference Blood Grouping Reagents shall be obtained from the Center for Biologics Evaluation and Research (HFN–890), 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 Blood Grouping Reagents.

(Information collection requirements approved by the Office of Management and Budget under control number 0910–0209)

§ 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-Jk^a, Anti-Fy^a, Anti-C^w, at least 1+ reaction with a 1:8 dilution of the reagent.

(2) For Anti-S, Anti-$\bar{s}$, Anti-P_1, Anti-M, Anti-I, Anti-e (saline), Anti-$\bar{c}$ (saline), and Anti-A_1, at least 1+ reaction with a 1:4 dilution of the reagent.

(3) For Anti-U, Anti-Kp^a, Anti-Kp^b, Anti-Js^a, Anti-Js^b, Anti-Fy^b, Anti-N, Anti-Le^a, Anti-Le^b, Anti-Lu^a, Anti-Lu^b, Anti-Di^a, Anti-M^g, Anti-Jk^b, Anti-Co^b, Anti-Wr^a, and Anti-Xg^a, at least 2+ reaction with undiluted 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 recomended 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 cells representing heterozygous or diminished expression of the corresponding antigen.

(Information collection requirements approved by the Office of Management and Budget under control number 0910–0209)

§ 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.

(Information collection requirements approved by the Office of Management and Budget under control number 0910–0209)

§ 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.

Blood grouping reagent	Color of label paper
Anti-A	Blue.
Anti-B	Yellow.
Slide and rapid tube test blood grouping reagents only:	
Anti-C	Pink.
Anti-D	Gray.
Anti-E	Brown.
Anti-CDE	Orange.
Anti-$\bar{c}$	Lavender.
Anti-e	Green.

(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.

(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 no less than 5 millimeters of the lower circumference to permit inspection of

the contents. The label on a final product container for antibodies Anti-c, Anti-k, or Anti-s shall display a bar immediately over the specificity letter used in the name, i.e., Anti-$\bar{c}$, Anti-k, or Anti-$\bar{s}$.

(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.

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

(3) Name, address (including ZIP Code), and license number of the manufacturer.

(4) Lot number, including sublot designations.

(5) Expiration date.

(6) Preservative used and its concentration.

(7) Number of containers, if more than one.

(8) Volume or equivalent volume for dried products when reconstituted, and precautions for adequate mixing when reconstituting.

(9) Recommended storage temperature in degrees Celsius.

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

(11) Reference to enclosed package insert.

(12) If a dried product, a statement indicating the period within which the product may be used after reconstitution.

(13) The statement: ''FOR IN VITRO DIAGNOSTIC USE.''

(14) The statement: ''MEETS FDA POTENCY REQUIREMENTS.''

(15) If human blood was used in manufacturing the product, 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.''

(16) 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.

(c) *Package insert.* Each final container of Blood Grouping Reagent shall be accompanied by a package insert meeting the requirements of §809.10. 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.*

Blood group designation for container label
Anti-A
Anti-A_1
Anti-A, B
Anti-A and B
Anti-B
Anti-C
Anti-C^w
Anti-c
Anti-CD
Anti-CDE
Anti-Co^b
Anti-D
Anti-DE
Anti-Di^a
Anti-E
Anti-e
Anti-Fy^a
Anti-Fy^b
Anti-I
Anti-Jk^a
Anti-Jk^b
Anti-Js^a
Anti-Js^b
Anti-K
Anti-k
Anti-Kp^a
Anti-Kp^b
Anti-Le^a
Anti-Le^b
Anti-Lu^a
Anti-Lu^b
Anti-M
Anti-M^g
Anti-N
Anti-P_1
Anti-S
Anti-s
Anti-U
Anti-Wr^a
Anti-Xg^a

[53 FR 12764, Apr. 19, 1988, as amended at 59 FR 23637, May 6, 1994]

(Information collection requirements approved by the Office of Management and Budget under control number 0910–0209)

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, or from umbilical cord cells which shall be collected and prepared according to the manufacturer's product 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 be collected as prescribed under § 640.4 of this chapter, except that paragraphs (c), (d), (g), and (h) of § 640.4 shall not apply.

§ 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 product 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, $\bar{c}$, e, K, k, Fy^a, Fy^b, Jk^a, Jk^b, Le^a, Le^b, P_1, M, N, S, and $\bar{s}$.

[52 FR 37450, Oct. 7, 1987, as amended at 55 FR 11013, Mar. 26, 1990]

§ 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 crossmatch, 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 lable 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 °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.

(f) *Retention samples.* Retention samples shall be maintained as required by § 600.13 of this chapter, except that samples must be retained only throughout the dating period of the product.

(Approved by the Office of Management and Budget under control number 0910–0073)

[52 FR 37450, Oct. 7, 1987, as amended at 55 FR 11013, Mar. 26, 1990]

§ 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, oustide 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.

(Approved by the Office of Management and Budget under control number 0910–0073)

§ 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-A_1, 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.

(Approved by the Office of Management and Budget under control number 0910–0073)

[52 FR 37450, Oct. 7, 1987, as amended at 55 FR 11013 and 11015, Mar. 26, 1990]

Subpart E—Hepatitis B Surface Antigen

SOURCE: 44 FR 36382, June 22, 1979, unless otherwise noted.

§ 660.40 Hepatitis B Surface Antigen.

(a) *Proper name and definition.* The proper name of this product shall be Hepatitis B Surface Antigen (HBsAg), which shall consist of a serum or tissue preparation containing one or more subtypes of the Hepatitis B Surface Antigen.

(b) *Source.* The source of the product shall be blood, plasma, serum, or tissue, obtained aseptically from nonhuman primates that have met the applicable requirements of §600.11 of this chapter, or from human donors whose blood is positive for the Hepatitis B Surface Antigen.

§ 660.41 Processing.

(a) *Method.* The processing method shall be one that has been shown to yield consistently a specific and potent final product, free of properties which would adversely affect the test results when the product is tested by the methods recommended by the manufacturer in the package insert. The product and all ancillary reagents and materials supplied in the package with the product shall be manufactured in a manner that will reduce the risk of transmitting type B viral hepatitis.

(b) *Ancillary reagents and materials.* All ancillary reagents and materials supplied in the package with the product shall meet generally accepted standards of purity and quality and shall be effectively segregated and otherwise manufactured in a manner that will reduce the risk of contaminating the product and other biological products. Ancillary reagents and materials accompanying the product, which are used in the performance of the test as described by the manufacturer's recommended test procedures, shall have been shown not to affect adversely the product within the prescribed dating period.

(c) *Final container.* A final container shall be sufficiently transparent to permit visual inspection of the contents for presence of particulate matter and increased turbidity. The effectiveness of the contents of a final container shall be maintained throughout its dating period.

(d) *Date of manufacture.* The date of manufacture of Hepatitis B Surface Antigen that has been iodinated with radioactive iodine (^{125}I) shall be the day of labeling the antibody with the radionuclide.

[44 FR 36382, June 22, 1979, as amended at 49 FR 1685, Jan. 13, 1984]

§ 660.42 Reference panel.

A Reference Hepatitis B Antiserum Panel shall be obtained from the Center for Biologics Evaluation and Research, 8800 Rockville Pike, Bethesda, MD 20892, and shall be used for determining the potency and specificity of Hepatitis B Surface Antigen.

[44 FR 36382, June 22, 1979, as amended at 49 FR 23834, June 8, 1984; 51 FR 15611, Apr. 25, 1986; 55 FR 11013, Mar. 26, 1990]

§ 660.43 Potency test.

To be satisfactory for release, each filling of Hepatitis B Surface Antigen shall be tested against the Reference Hepatitis B Antiserum Panel and shall be sufficiently potent to be able to detect the antibody in the appropriate sera of the reference panel by all test methods recommended by the manufacturer in the package insert.

§ 660.44 Specificity.

Each filling of the product shall be specific for Hepatitis B Surface Antigen as determined by specificity tests found acceptable to the Director, Center for Biologics Evaluation and Research.

[44 FR 36382, June 22, 1979, as amended at 49 FR 23834, June 8, 1984; 55 FR 11013, Mar. 26, 1990]

§ 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.

§ 660.46 Samples; protocols; official release.

(a) *Samples.* (1) For the purposes of this section, a sample of product not iodinated with ^{125}I 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 ^{125}I 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.

(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.

[48 FR 20407, May 6, 1983, as amended at 49 FR 23834, June 8, 1984; 51 FR 15611, Apr. 25, 1986; 55 FR 11013 and 11014, Mar. 26, 1990]

Subpart F—Anti-Human Globulin

§ 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) and be

prepared by a method demonstrated to yield consistently a sterile product.

(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.

[50 FR 5579, Feb. 11, 1985]

§ 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 sterile filtered shall constitute a lot. Each lot shall be identified by a lot number.

(4) A lot may be subdivided into clean, sterile vessels. Each subdivision shall constitute a sublot 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 and on the protocol. 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.

(Approved by the Office of Management and Budget under control number 0910–0208)

[50 FR 5579, Feb. 11, 1985, as amended at 50 FR 16474, Apr. 26, 1985]

§ 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.

(Approved by the Office of Management and Budget under control number 0910–0208)

[50 FR 5579, Feb. 11, 1985, as amended at 50 FR 16474, Apr. 26, 1985; 51 FR 15611, Apr. 25, 1986; 55 FR 11015, Mar. 26, 1990]

§ 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.

(Approved by the Office of Management and Budget under control number 0910–0208)

[50 FR 5579, Feb. 11, 1985, as amended at 50 FR 16474, Apr. 26, 1985; 51 FR 15611, Apr. 25, 1986; 55 FR 11014, Mar. 26, 1990]

§ 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.

(Approved by the Office of Management and Budget under control number 0910–0208)

[50 FR 5579, Feb. 11, 1985, as amended at 50 FR 16474, Apr. 26, 1985; 51 FR 15611, Apr. 25, 1986; 55 FR 11014, Mar. 26, 1990]

§ 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.*

Antibody designation on container label	Definition
(1) Anti-IgG, -C3d; Polyspecific.	Contains anti-IgG and anti-C3d (may contain other anticomplement and anti-immunoglobulin antibodies).
(2) Anti-IgG	Contains anti-IgG with no anti-complement activity (not necessarily gamma chain specific).
(3) Anti-IgG; heavy chains.	Contains only antibodies reactive against human gamma chains.
(4) Anti-C3b	Contains only C3b antibodies with no anti-immunoglobulin activity. **Note:** 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.
(5) Anti-C3d	Contains only C3d antibodies with no anti-immunoglobulin activity.
(6) Anti-C4b	Contains only C4b antibodies with no anti-immunoglobulin activity.
(7) Anti-C4d	Contains only C4d antibodies with no anti-immunoglobulin activity.

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.

(Approved by the Office of Management and Budget under control number 0910–0208)

[50 FR 5579, Feb. 11, 1985; 50 FR 9800, Mar. 12, 1985, as amended at 50 FR 16474, Apr. 26, 1985; 55 FR 11014, Mar. 26, 1990]

Subparts G–J—[Reserved]

Subpart K—Limulus Amebocyte Lysate

§ 660.100 Limulus Amebocyte Lysate.

The proper name of this product shall be Limulus Amebocyte Lysate. The product is defined as an extract that is derived from the blood of *Limulus polyphemus* and is capable of detecting bacterial endotoxins.

[45 FR 32299, May 16, 1980]

§ 660.101 U.S. Standard/Reference Preparations.

The following U.S. Standard/Reference preparations shall be obtained from the Center for Biologics Evaluation and Research, Food and Drug Administration, 8800 Rockville Pike, Bethesda, MD 20892, for use as prescribed in this subpart:

(a) A U.S. Standard Endotoxin for determining the sensitivity of Limulus Amebocyte Lysate.

(b) A U.S. Reference Limulus Amebocyte Lysate for establishing the potency of Limulus Amebocyte Lysate.

[45 FR 32299, May 16, 1980, as amended at 49 FR 23834, June 8, 1984; 51 FR 15611, Apr. 25, 1986; 55 FR 11013, Mar. 26, 1990]

§ 660.102 Potency test.

A sample of each final filling of each lot of Limulus Amebocyte Lysate and the U.S. Reference Lysate shall be tested in parallel with the U.S. Standard Endotoxin. If the product is freeze-dried after filling, the test shall be conducted on samples from each filling in each drying chamber run. The procedure for rehydrating and mixing the lysate for the potency test shall be that specified in the manufacturer's package insert. A minimum of 8 vials and a maximum of 28 vials from each filling or, if freeze-dried, from each drying chamber run representing all parts of the chamber load, shall be tested in parallel with an equal number of tests from 1 or more vials of the U.S. Reference Lysate. The test shall be performed as follows:

(a) *Dilution of U.S. Standard Endotoxin.* A single series of consecutive two-fold dilutions, beginning with a concentration of the U.S. Standard Endotoxin at least four-fold above the endpoint, shall be prepared with a range selected to bracket the endpoint for both the U.S. Reference Lysate and test lysate filling in each test performed.

(b) *Test procedure.* (1) Transfer 0.1 milliliter of each concentration of U.S. Standard Endotoxin, as prepared in paragraph (a) of this section, into each of two test tubes having an inside diameter not greater than 10 millimeters, unless the use of another size test

tube has been approved by the Director, Center for Biologics Evaluation and Research.

(2) Add 0.1 milliliter of the U.S. Reference Lysate to one of the tubes containing the lowest concentration of U.S. Standard Endotoxin. Add 0.1 milliliter of test lysate to the second tube containing the lowest concentration of U.S. Standard Endotoxin.

(3) Repeat the procedure in paragraphs (b)(1) and (2) of this section for each dilution of the U.S. Standard Endotoxin and for each vial of lysate to be tested from each filling of the test lot, progressing from the lowest endotoxin concentration to the highest.

(4) Immediately following addition of the lysate to each tube, mix the contents gently and place in a 37° C water bath for 1 hour.

(c) *Validity of the test.* (1) Record the reaction in each tube as either positive or negative. A positive reaction is demonstrated by a firm gel that remains intact, at least momentarily, when the tube is inverted 180 degrees. For Limulus Amebocyte Lysate that does not require gelation as an indicator of reactions, the endpoint shall be determined by the method specified in the labeling for the product.

(2) For each parallel test obtain the ratio of endpoints of reference and test lysates. Calculate the standard deviations (S.D.) of log ratios.

(3) The test is valid if the S.D. is less than or equal to the value for the 99 percent fiducial upper limit of the S.D. of the sample size tested. The S.D. table is shown in paragraph (d) of this section.

(4) If the S.D. is greater than the tabulated value, the test may be expanded up to the maximum of 28 parallel tests and a new S.D. for log ratios may be calculated.

(5) The tests are invalid due to excessive variability if the S.D. is greater than the value in the S.D. table corresponding to the sample size tested.

(6) If the S.D. is within the limits, the geometric mean (G.M.) of the ratios shall be calculated.

(7) The endpoints of U.S. Reference and test lysates, ratios of endpoints, S.D. of log ratios, and G.M. of ratios shall be calculated and reported on the protocol submitted to the Director, Center for Biologics Evaluation and Research.

(d) *S.D. table.* Ninety-nine percent fiducial upper limit on S.D. of $\log_2$ (ratio):

Sample size	Upper limit
4	[1] 1.02
8	0.86
12	0.79
16	0.75
20	0.73
24	0.71
28	0.69

[1] Limits can be converted to $\log_{10}$ by multiplying each value by 0.3.

[45 FR 32299, May 16, 1980, as amended at 49 FR 23834, June 8, 1984; 52 FR 39637, Oct. 23, 1987; 55 FR 11013, Mar. 26, 1990]

§ 660.103 General requirements.

(a) *Handling the horseshoe crabs.* The horseshoe crabs (*Limulus polyphemus*), from which blood is collected for production of the lysate, shall be handled in a manner so as to minimize injury to each crab. The horseshoe crabs shall be returned alive to their natural environment after a single collection of their blood.

(b) *Processing.* The processing methods shall be those which have been shown to yield consistently a potent and detection-specific final product free of properties that would adversely affect the accuracy of the test results when the Limulus Amebocyte Lysate is used by the methods recommended by the manufacturer in the package insert.

(c) *Final containers.* Final containers at the time of filling shall be sterile, nonpyrogenic, colorless, and transparent.

(d) *Date of manufacture.* The date of manufacture of each filling of each lot shall be the date the manufacturer initiated the last valid potency test for such filling. The results from this test shall be reported on the protocol submitted to the Director, Center for Biologics Evaluation and Research.

(e) *Sterility test.* A sterility test shall be performed on the bulk lot and on each filling as prescribed in §610.12 of this chapter.

(f) *Test for quality.* A test for lysate quality shall be performed as follows:

(1) Samples from each of eight final containers from each filling or, if freeze-dried, from each filling in each drying chamber run representing all parts of the chamber load, shall be used.

(2) The volume of lysate required for a single test from each of the final containers and a volume of distilled water equal to the volume of sample used for a single test are combined into each of an appropriate number of test tube and incubated for 24 hours in a 37° C water bath.

(3) The test passes if none of the samples yield a positive test.

(g) *Test for residual moisture.* (1) If the weight of the contents of each final container is 3 milligrams or more, the test for residual moisture shall be performed as prescribed in §610.13(a) of this chapter.

(2)(i) If the weight of the contents of each final container is less than 3 milligrams, the product is exempt from the test for residual moisture. However, the manufacturer of such exempt product shall perform the potency test described in §660.102 on at least 4 vials at 4-month intervals on representative samples from each filling throughout the dating period.

(ii) Upon the completion of each potency test, the results of all tests performed shall be submitted to the Director, Center for Biologics Evaluation and Research.

(h) *Ancillary reagents and materials.* All ancillary reagents and materials accompanying the product that are used in the performance of a test, as described by the manufacturer's recommended test procedures, shall not affect adversely the performance of the Limulus Amebocyte Lysate within the prescribed dating period.

[45 FR 32299, May 16, 1980, as amended at 49 FR 23834, June 8, 1984; 52 FR 39637, Oct. 23, 1987; 55 FR 11013, Mar. 26, 1990]

§ 660.104 Labeling.

In addition to the applicable labeling provisions of this chapter, the following information is required:

(a) *Final container labels.* The final container label shall include the following additional information:

(1) The sensitivity (geometric mean of the end points of the lot) expressed as units/milliliter or nanograms/milliliter of the U.S. Standard Endotoxin, determined by the potency test procedure in §660.102.

(2) For final containers intended for multiple tests, a designated area adequate for the user to identify the time that the product is reconstituted.

(3) For final containers intended for multiple tests, a statement identifying the period within which the product may be used after reconstitution.

(4) For final containers intended for multiple tests, a statement specifying storage conditions after reconstitution.

(b) *Package label.* The package label shall include the following additional information:

(1) A reference to the package insert for the test method(s) to be employed when using Limulus Amebocyte Lysate.

(2) A statement that the product shall not be rehydrated until immediately prior to use.

(3) For products in final containers intended for multiple tests, a statement identifying the period within which the product may be used after reconstitution.

(4) For products in final containers intended for multiple tests, a statement specifying storage conditions after reconstitution.

(c) *Package insert.* The package insert shall include the following additional information:

(1) A statement that if the container of diluent used to rehydrate the lysate has been entered previously or was not supplied by the manufacturer of the lysate, the diluent must be tested, without addition of test material.

(2) A warning statement that the tubes of material on test should not be removed from incubation or disturbed prior to the time specified for reading the test.

(3) A statement that the product shall not be rehydrated until immediately prior to use.

(4) For products in final containers intended for multiple tests, a statement identifying the period within which the product may be used after reconstitution.

(5) For products in final containers intended for multiple tests, a statement specifying storage conditions after reconstitution.

[45 FR 32299, May 16, 1980]

§ 660.105 Samples and protocols; official release.

(a) For each final filling of each lot of Limulus Amebocyte Lysate, or if freeze dried, from each drying chamber run representing all parts of the chamber load, the following material shall be submitted to the Director, Center for Biologics Evaluation and Research, Food and Drug Administration, 8800 Rockville Pike, Bethesda, MD 20892:

(1) *Samples.* Not fewer than the number of vials of lysate used for the potency test in § 660.102, two of which shall be complete market packages, packaged for distribution and including all ancillary reagents and materials.

(2) *Protocols.* A protocol consisting of a complete summary of the history of manufacture of each filling, the dates of testing, and the results of all required tests.

(b) *Official release.* Limulus Amebocyte Lysate shall not be distributed by the manufacturer until written notification of official release of each filling is received from the Director, Center for Biologics Evaluation and Research.

[45 FR 32299, May 16, 1980, as amended at 49 FR 23834, June 8, 1984; 51 FR 15611, Apr. 25, 1986; 52 FR 39637, Oct. 23, 1987; 55 FR 11013, Mar. 26, 1990]

PART 680—ADDITIONAL STANDARDS FOR MISCELLANEOUS PRODUCTS

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AUTHORITY: Secs. 201, 501, 502, 503, 505, 510, 701 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, 351, 352, 353, 355, 360, 371); secs. 215, 351, 352, 353, 361 of the Public Health Service Act (42 U.S.C. 216, 262, 263, 263a, 264).

SOURCE: 38 FR 32100, 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—Allergenic Products

§ 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 postmortal decomposition processes do not adversely affect the allergen, and (*b*) when alive, the animal met the applicable requirements prescribed in paragraphs (b)(3) (i), (ii), and (iii) of this section.

(vi) *Mammals and birds inspected by the U.S. Department of Agriculture.* Mammals and birds, subject to inspection by the U.S. Department of Agriculture at the time of slaughter and found suitable as food, may be used as a source material, and the requirements of paragraph (b)(3) (i) through (iv) of this section do not apply in such a case. Notwithstanding U.S. Department of Agriculture inspection, the carcasses of such inspected animals shall be frozen or kept cold until the allergen is collected, or shall be stored under other acceptable conditions so that the postmortal decomposition processes do not adversely affect the allergen.

(c) *Listing of source materials and suppliers.* Each licensed manufacturer shall initially list with the Director, Center for Biologics Evaluation and Research (HFB–1), the name and address of each of the manufacturer's source material suppliers. The listing shall identify each source material obtained from each source material supplier. The licensed manufacturers shall update the listing annually to include new source material suppliers or to delete those no longer supplying source materials.

(d) *Exemptions.* (1) Exemptions or modifications from the requirements under paragraph (b) of this section shall be made only upon written approval by the Director, Center for Biologics Evaluation and Research (HFB–1).

(2) Nonlicensed source material suppliers are exempt from drug registration.

(Approved by the Office of Management and Budget under control number 0910–0124 for paragraph (b)(2)(iii) and control number 0910–0161 for paragraph (c))

[38 FR 32100, Nov. 20, 1973, as amended at 49 FR 25432, June 21, 1984; 49 FR 31395, Aug. 7, 1984; 55 FR 11014, Mar. 26, 1990]

§ 680.2 Manufacture of Allergenic Products.

(a) *Extraneous allergenic substances.* All manufacturing steps shall be performed so as to insure 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 (OMB control number 0910–0139) 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.

[38 FR 32100, Nov. 20, 1973, as amended at 49 FR 25433, June 21, 1984]

§ 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 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.

(Information collection requirements in this section were approved by the Office of Management and Budget under control number 0910–0139)

[38 FR 32100, Nov. 20, 1973, as amended at 39 FR 19777, June 6, 1974; 41 FR 4015, Jan. 28, 1976; 52 FR 37607, Oct. 8, 1987; 55 FR 11013, Mar. 26, 1990]

Subpart B—Trivalent Organic Arsenicals

§ 680.10 Tests prior to release.

Tests required to be made, prior to the release of each lot of a licensed product, shall be supplemented in the case of the trivalent organic arsenicals by tests for:

(a) Stability,

(b) Solubility,

(c) Arsenic content,

(d) Moisture,

(e) Relative nontoxicity.

§ 680.11 Pretesting by Center; sample of each lot.

Prior to the release of any lot of the product, the manufacturer shall forward to the Director, Center for Biologics Evaluation and Research, no less than 15 ampoules of the largest single-dose size in such lot, together with protocols showing the results of each test required prior to release.

[38 FR 32100, Nov. 20, 1973, as amended at 49 FR 23834, June 8, 1984; 55 FR 11013, 11015, Mar. 26, 1990]

§ 680.12 Expiration date.

Notification from the Director, Center for Biologics Evaluation and Research, that lot samples forwarded in accordance with § 680.11 have satisfactorily passed prescribed tests shall indicate a date which may be taken as the date of manufacture for the purpose of fixing the expiration date. The date of issue shall be the same as the date of manufacture.

[38 FR 32100, Nov. 20, 1973, as amended at 49 FR 23834, June 8, 1984; 55 FR 11013, Mar. 26, 1990]

§ 680.13 Composition of product.

Solutions or solutions of mixtures in the concentrations recommended for clinical administration shall be of such hydrogen ion value and tonicity as to be physiologically compatible with human blood.

§ 680.14 Container.

The product shall be hermetically sealed under vacuum or under a dry nonoxidizing gas in glass ampoules. The contents of any final container shall not exceed 10 maximum human doses.

§ 680.15 Final container label.

In addition to the labeling requirements stated in § 610.60 of this chapter, the final container label of the trivalent organic arsenicals shall bear the statements required in § 680.16 (b) and (c) and an additional statement giving the amount of the drug contained in the ampoule.

§ 680.16 Outside label.

The outside label, in addition to the complete proper name and all other items required for products generally shall show conspicuously:

(a) If the product is dispensed as a mixture or solution, the name of all admixed substances.

(b) If the ampoule is a multiple dose container, the fact that it is a multiple dose container.

(c) Specific method of preparation, if any, required prior to administration, as, for example alkalinization.

Subpart C—Blood Group Substances

SOURCE: 44 FR 20674, Apr. 6, 1979, unless otherwise noted.

§ 680.20 Blood Group Substances.

(a) *Proper names and definitions.* The proper names of these products shall be Blood Group Substance A, Blood Group Substance B, and Blood Group Substance AB. Each Blood Group Substance product shall consist of a sterile, pyrogen-free, nonanaphylactogenic, aqueous solution of purified polysaccharideamino acid complexes for use in immunization.

(b) *Source.* Blood Group Substance A shall be prepared from porcine stomachs; Blood Group Substance B and Blood Group Substance AB shall be prepared from equine stomachs.

§ 680.21 Reference preparations.

The following reference preparations shall be obtained from the Center for Biologics Evaluation and Research, Food and Drug Administration, 8800 Rockville Pike, Bethesda, MD 20892, for use in determining the potency of Blood Group Substance as described in § 680.22 and in the manufacturer's package insert:

Reference Anti-A Blood Grouping Serum.
Reference Anti-B Blood Grouping Serum.
Reference Blood Group Substance A.
Reference Blood Group Substance B.

[44 FR 20674, Apr. 6, 1979; 48 FR 13026, Mar. 29, 1983, as amended at 49 FR 23834, June 8, 1984; 51 FR 15611, Apr. 25, 1986; 55 FR 11013, Mar. 26, 1990]

§ 680.22 Potency and identity tests.

An inhibition test for potency shall be performed on the contents of a final container of each lot of each product as follows:

(a) *Cell suspensions.* Separate 1 percent suspensions of A_1 and B red blood cells in isotonic saline shall be prepared daily after washing the cells at least twice with isotonic saline and shall result in a clear supernate. The cell suspensions shall be prepared from blood within 7 days after collection.

(b) *Reference serum.* (1) Reference Anti-A and Reference Anti-B Blood Grouping Serums shall be used in the inhibition test.

(2) Twofold dilutions (1:2, 1:4, 1:8, etc.) of each of the reference serums shall be prepared in isotonic saline containing a final concentration of 1 to 2 percent bovine albumin.

(3) A clean pipette shall be used for each dilution and each serum. Mechanical devices that avoid carryover may be used.

(c) *The test for selection of serum dilution for use in the inhibition test for potency.* (1) Reference Anti-A and Anti-B Blood Grouping Serums shall each be tested using A_1 and B cells, respectively.

(2) To a series of clean small test tubes (approximately 10 x 75 millimeters), add 0.1 milliliter of each successive serum dilution prepared as described in paragraph (b)(2) of this section and 0.1 milliliter of the appropriate 1 percent cell suspension prepared as described in paragraph (a) of this section.

(3) Mix thoroughly and centrifuge immediately for 1 minute at approximately 150 relative centrifuge force (rcf) or at approximately 1,000 rcf for 20 seconds.

(d) *Interpretation of the test.* The cell buttons shall be gently dislodged and observed macroscopically. The reactions shall be graded as follows:

4+ Cell button remains in one clump.
3+ Cell button dislodges into several clumps.
2+ Cell button dislodges into many small clumps of nearly equal size.
1+ Cell button dislodges into finely granular, but definite, small clumps.

(e) *Selection of serum dilution for use in the inhibition test.* The proper dilution

of the reference serum for use in the inhibition test is the next to the highest dilution showing a 4+ agglutination reaction (e.g., with the following dilution/reaction table:

Dilution	Un.	1:2	1:4	1:8	1:16	1:32	1:64	1:128	1:256	1:512
Reaction	4+	4+	4+	4+	4+	3+	2+	1+	0	0

the proper dilution is 1:8).

(f) *Preparation for the inhibition test for potency*—(1) *Reference serum dilution.* A minimum of 3 milliliters of Reference Blood Grouping Serum shall be prepared in a proper dilution as described in paragraph (e) of this section.

(2) *Blood Group Substance dilution.* (i) A series of 11 separate threefold dilutions (1:3, 1:9, 1:27, etc.) of Blood Group Substance shall be prepared in isotonic saline in concentrations ranging from 1:1 (undiluted) to 1:59, 049.

(ii) A clean pipette shall be used for each dilution. Mechanical devices that avoid carryover may be used.

(g) *Performance of the inhibition tests for potency*—(1) *Blood Group Substance A.* (i) Transfer 0.1 milliliter of each dilution of Blood Group Substance A prepared as described in paragraph (f)(2) of this section to each one of 11 small test tubes (approximately 10 x 75 millimeters).

(ii) Place 0.1 milliliter of isotonic saline into a 12th test tube.

(iii) To each of the 12 test tubes, add 0.1 milliliter of the properly diluted Reference Anti-A Blood Grouping Serum prepared as described in paragraph (f)(1) of this section.

(iv) Mix thoroughly and incubate at room temperature (20° to 24° C) for 10 minutes.

(v) To each of the 12 test tubes, add 0.1 milliliter of the 1 percent A_1 cell suspension described in paragraph (a) of this section.

(vi) Mix gently and incubate at room temperature (20° to 24° C) for 15 minutes.

(vii) Centrifuge for 1 minute at approximately 150 relative centrifugal force (rcf) or at approximately 1,000 rcf for 20 seconds.

(viii) Repeat steps in paragraphs (g)(1)(i) through (vii) of this section using Reference Blood Group Substance A.

(ix) Repeat steps in paragraphs (g)(1)(i) through (vii) of this section using Reference Anti-B Blood Grouping Serum, the B cell suspension, and the Blood Group Substance A under test.

(2) *Blood Group Substance B.* For Blood Group Substance B or for Blood Group Substance AB, repeat steps in paragraphs (g)(1)(i) through (vii) of this section, using each of the following sets of reagents.

(i) Blood Group Substance B plus Reference Anti-B Blood Grouping Serum plus B cell suspension.

(ii) Blood Group Substance B plus Reference Anti-A Blood Grouping Serum plus A_1 cell suspension.

(iii) Reference Blood Group Substance B plus Reference Anti-B Blood Grouping Serum plus B cell suspension.

(iv) Reference Blood Group Substance A plus Reference Anti-A Blood Grouping Serum plus A_1 cell suspension.

(h) *Interpretation of the test.* The cell buttons shall be gently dislodged and observed macroscopically. The reactions shall be graded as described in paragraph (d) of this section. The highest dilution of Blood Group Substance that totally inhibits agglutination is taken as the inhibition end point.

(i) *Potency test requirements.* Blood Group Substance A shall have a potency inhibition titer value equal to or greater than that of the Reference Blood Group Substance A. Blood Group Substance B shall have a potency inhibition titer value equal to or greater than that of the Reference Blood Group Substance B and less than that of Reference Blood Group Substance A. Blood Group Substance AB shall have potency inhibition titer values equal to or greater than those of Reference Blood Group Substance A and Reference Blood Group Substance B.

§680.23 Other tests.

(a) *Safety.* A safety test shall be performed on the contents of final containers of each lot of each product as prescribed in §610.11 of this chapter.

(b) *Sterility.* A sterility test shall be performed on the contents of final containers of each lot of each product as prescribed in § 610.12 of this chapter.

(c) *Pyrogens.* A pyrogen test shall be performed on the contents of final containers of each lot of each product as prescribed in § 610.13(b) of this chapter.

(d) *Anaphylaxis.* An anaphylactic test shall be performed on the contents of a sufficient number of final containers of each lot of each product to perform the test as follows:

(1) The contents of one final container shall be injected intraperitoneally into each of 10 normal guinea pigs.

(2) After 3 weeks, each guinea pig shall be challenged intravenously with a 0.2-milliliter sample of the same product.

(3) None of the 10 sensitized guinea pigs shall exhibit anaphylactic shock.

§ 680.24 General requirements.

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

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

(3) Each lot shall be filled in a single continuous operation.

(b) *Total nitrogen.* Blood Group Substances shall contain not more than 8 percent total nitrogen when determined on moisture-free and ash-free samples.

(c) *Preservative.* A preservative shall not be incorporated into bulk manufactured Blood Group Substance or into final containers. However, phenol may be present as a residual from manufacturing.

(d) *Final containers.* Final containers shall be sterile, pyrogen free, colorless, and transparent. The contents of the final container shall not exceed 1 milliliter of product containing not more than one immunizing dose of Blood Group Substance powder.

(e) *Date of manufacture.* The date of manufacture shall be the date the manufacturer initiates the last valid potency test that is reported on a protocol and submitted to the Director, Center for Biologics Evaluation and Research.

(f) *Dose.* A single human dose for intramuscular, subcutaneous or intradermal injection shall not exceed the contents of a final container.

[44 FR 20674, Apr. 6, 1979; 48 FR 13026, Mar. 29, 1983, as amended at 49 FR 23834, June 8, 1984; 55 FR 11013, Mar. 26, 1990]

§ 680.25 Labeling.

In addition to the labeling requirements of § 610.62 of this chapter and in lieu of the requirements in §§ 610.60 and 610.61 of this chapter, the following shall appear on the label of Blood Group Substances:

(a) *Label affixed to each final container.* (1) Proper name of the product.

(2) Name, address (including zip code), and license number of the manufacturer.

(3) Lot number.

(4) Expiration date.

(5) The statement ''ONE IMMUNIZING DOSE''.

(6) Recommended storage temperature.

(7) The statement ''SEE DIRECTIONS FOR USE''.

(b) *Container not enclosed in a package.* If the final container is not enclosed in a package, e.g., the container is enclosed only in an unlabeled shipping carton, all information required for the package label in paragraph (c) of this section shall accompany and be attached to each final container.

(c) *Package label.* (1) Proper name of the product.

(2) Name, address (including zip code), and license number of the manufacturer.

(3) Lot number.

(4) Expiration date.

(5) The statement ''CONTAINS NO PRESERVATIVE''.

(6) Number of containers, if more than one.

(7) The statement ''DERIVED FROM PORCINE (OR EQUINE) STOMACHS'', as applicable.

(8) The statement ''EACH FINAL CONTAINER CONTAINS ONE IMMUNIZING DOSE''.

(9) Recommended storage temperature.

(10) The statement ''DO NOT ADMINISTER INTRAVENOUSLY''.

(11) The statement ''DO NOT ADMINISTER TO FERTILE WOMEN''.

(12) Recommendations for use.

(13) For Blood Group Substance B, the statement ''CAUTION: MAY CONTAIN IMMUNOGENIC A ACTIVITY''.

(14) The statement ''CAUTION: FEDERAL LAW PROHIBITS DISPENSING WITHOUT A PRESCRIPTION''.

(15) Reference to enclosed package insert.

§ 680.26 Samples; protocols; official release.

For each lot of product, the following material shall be submitted to the Director, Center for Biologics Evaluation and Research, Food and Drug Administration, 8800 Rockville Pike, Bethesda, MD 20892:

(a) *Samples.* Randomly selected samples consisting of 40 final containers packaged for distribution.

(b) *Protocol.* A protocol consisting of a summary of the history of the manufacture of the product, including the dates and results of all tests that are required by regulations.

(c) *Official release.* The product shall not be issued by the manufacturer until written notification of official release is received from the Director, Center for Biologics Evaluation and Research.

[44 FR 20674, Apr. 6, 1979; 48 FR 13026, Mar. 29, 1983, as amended at 49 FR 23834, June 8, 1984; 51 FR 15611, Apr. 25, 1986; 55 FR 11013, Mar. 26, 1990]

SUBCHAPTER G—COSMETICS

PART 700—GENERAL

Subpart A—General Provisions

Subpart B—Requirements for Specific Cosmetic Products

AUTHORITY: Secs. 201, 301, 502, 505, 601, 602, 701, 704 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, 331, 352, 355, 361, 362, 371, 374).

SOURCE: 39 FR 10054, Mar. 15, 1974, unless otherwise noted.

Subpart A—General Provisions

§ 700.3 Definitions.

As used in this subchapter:

(a) The term *act* means the Federal Food, Drug, and Cosmetic Act.

(b) The term *cosmetic product* means a finished cosmetic the manufacture of which has been completed. Any cosmetic product which is also a drug or device or component thereof is also subject to the requirements of Chapter V of the act.

(c) The term *flavor* means any natural or synthetic substance or substances used solely to impart a taste to a cosmetic product.

(d) The term *fragrance* means any natural or synthetic substance or substances used solely to impart an odor to a cosmetic product.

(e) The term *ingredient* means any single chemical entity or mixture used as a component in the manufacture of a cosmetic product.

(f) The term *proprietary ingredient* means any cosmetic product ingredient whose name, composition, or manufacturing process is protected from competition by secrecy, patent, or copyright.

(g) The term *chemical description* means a concise definition of the chemical composition using standard chemical nomenclature so that the chemical structure or structures of the components of the ingredient would be clear to a practicing chemist. When the composition cannot be described chemically, the substance shall be described in terms of its source and processing.

(h) The term *cosmetic raw material* means any ingredient, including an ingredient that is a mixture, which is used in the manufacture of a cosmetic product for commercial distribution and is supplied to a cosmetic product manufacturer, packer, or distributor by a cosmetic raw material manufacturer or supplier.

(i) The term *commercial distribution* of a cosmetic product means annual gross sales in excess of $1,000 for that product.

(j) *Establishment* means a place of business where cosmetic products are manufactured or packaged.

(k) The term *manufacture* of a cosmetic product means the making of any cosmetic product by chemical, physical, biological, or other procedures, including manipulation, sampling, testing, or control procedures applied to the product.

(l) The term *packaging* of a cosmetic product means filling or labeling the product container, including changing the immediate container or label (but excluding changing other labeling) at any point in the distribution of the cosmetic product from the original place of manufacture to the person who makes final delivery or sale to the ultimate consumer.

(m) The term *all business trading names used by the establishment* means any name which is used on a cosmetic product label and owned by the cosmetic product manufacturer or packer, but is different from the principal name under which the cosmetic product manufacturer or packer is registered.

(n) The definitions and interpretations contained in sections 201, 601, and 602 of the act shall be applicable to such terms when used in the regulations in this subchapter.

(o) *System of commercial distribution* of a cosmetic product means any distribution outside the establishment manufacturing the product, whether for sale, to promote future sales (including free samples of the product), or to gage consumer acceptance through market testing, in excess of $1,000 in cost of goods.

(p) *Filed screening procedure* means a procedure that is:

(1) On file with the Food and Drug Administration and subject to public inspection;

(2) Designed to determine that there is a reasonable basis for concluding that an alleged injury did not occur in conjunction with the use of the cosmetic product; and

(3) Which is subject, upon request by the Food and Drug Administration, to an audit conducted by the Food and Drug Administration at reasonable times and, where an audit is conducted, such audit shows that the procedure is consistently being applied and that the procedure is not disregarding reportable information.

(q) *Reportable experience* means an experience involving any allergic reaction, or other bodily injury, alleged to be the result of the use of a cosmetic product under the conditions of use prescribed in the labeling of the product, under such conditions of use as are customary or reasonably foreseeable for the product or under conditions of misuse, that has been reported to the manufacturer, packer, or distributor of the product by the affected person or any other person having factual knowledge of the incident, other than an alleged experience which has been determined to be unfounded or spurious when evaluated by a filed screening procedure.

[39 FR 10054, Mar.15, 1974, as amended at 46 FR 38073, July 24, 1981]

Subpart B—Requirements for Specific Cosmetic Products

§ 700.10 Shampoo preparations containing eggs as one of the ingredients.

The present views of the Food and Drug Administration concerning the status of shampoo preparations containing egg as one of the ingredients are as follows:

(a) An article designated as ''egg shampoo'' should contain one egg (or the equivalent amount of dried whole egg) in that quantity of the article which would be used in one shampooing of the hair.

(b) An article that contains less than one egg per ''shampoo'' should not be referred to as an ''egg shampoo'' and the word ''egg'' should not be used as part of the name of the article. At the present time, the Food and Drug Administration is not raising objection to the marketing of an article containing less than one egg per ''shampoo,'' provided the word ''egg'' does not appear in the name of the article, the reference to the egg ingredient, such as ''plus egg,'' appears in a subordinate position on the label and is in type which is substantially reduced in size in comparison with the title of the article, and the reference to the presence of egg reveals the amount of the egg ingredient.

(c) In the case of an article containing less than 2 percent egg, the amount of egg is so small as to be insignificant, and it is therefore considered that it would be misleading for the labeling to make any mention of the presence of egg in such a product.

§ 700.11 Cosmetics containing bithionol.

(a) Bithionol has been used to some extent as an antibacterial agent in cosmetic preparations such as detergent bars, shampoos, creams, lotions, and bases used to hide blemishes. New evidence of clinical experience and photopatch tests indicate that bithionol is capable of causing

photosensitivity in man when used topically and that in some instances the photosensitization may persist for prolonged periods as severe reactions without further contact with sensitizing articles. Also, there is evidence to indicate that bithionol may produce cross-sensitization with other commonly used chemicals such as certain halogenated salicylanilides and hexachlorophene. It is, therefore, the view of the Food and Drug Administration that bithionol is a deleterious substance which may render any cosmetic product that contains it injurious to users. Accordingly, any cosmetic containing bithionol is deemed to be adulterated under section 601(a) of the Federal Food, Drug, and Cosmetic Act.

(b) Regulatory proceedings may be initiated with respect to any cosmetic preparation containing bithionol shipped within the jurisdiction of the act after March 15, 1968.

§ 700.13 Use of mercury compounds in cosmetics including use as skinbleaching agents in cosmetic preparations also regarded as drugs.

(a) Mercury-containing cosmetic preparations have been represented for many years as skin-bleaching agents or as preparations to remove or prevent freckles and/or brown spots (so-called age spots). Preparations intended for such use are regarded as drugs as well as cosmetics. In addition to such use as skin-bleaching agents, mercury compounds have also been widely used as preservatives in cosmetics such as hand and body creams and lotions; hair shampoos, hair sets and rinses, hair straighteners, hair coloring, and other preparations; bath oils, bubble bath, and other bath preparations; makeup; antiperspirants and deodorants; and eye-area cosmetics.

(b) The toxicity of mercury compounds is extensively documented in scientific literature. It is well known that mercury compounds are readily absorbed through the unbroken skin as well as through the lungs by inhalation and by intestinal absorption after ingestion. Mercury is absorbed from topical application and is accumulated in the body, giving rise to numerous adverse effects. Mercury is a potent allergen and sensitizer, and skin irritation is common after topical application. Cosmetic preparations containing mercury compounds are often applied with regularity and frequency for prolonged periods. Such chronic use of mercury-containing skin-bleaching preparations has resulted in the accumulation of mercury in the body and the occurrence of severe reactions. Recently it has also been determined that microorganisms in the environment can convert various forms of mercury into highly toxic methyl mercury which has been found in the food supply and is now considered to be a serious environmental problem.

(c) The effectiveness of mercury-containing preparations as skin-bleaching agents is questionable. The Food and Drug Administration has not been provided with well controlled studies to document the effectiveness of these preparations. Although mercurial preservatives are recognized as highly effective, less toxic and satisfactory substitutes are available except in the case of certain eye-area cosmetics.

(d) Because of the known hazards of mercury, its questionable efficacy as a skin-bleaching agent, and the availability of effective and less toxic nonmercurial preservatives, there is no justification for the use of mercury in skin-bleaching preparations or its use as a preservative in cosmetics, with the exception of eye-area cosmetics for which no other effective and safe nonmercurial preservative is available. The continued use of mercurial preservatives in such eye-area cosmetics is warranted because mercury compounds are exceptionally effective in preventing *Pseudomonas* contamination of cosmetics and *Pseudomonas* infection of the eye can cause serious injury, including blindness. Therefore:

(1) The Food and Drug Administration withdraws the opinion expressed in trade correspondence TC–9 (issued May 13, 1939) and concludes that any product containing mercury as a skin-bleaching agent and offered for sale as skin-bleaching, beauty, or facial preparation is misbranded within the meaning of sections 502(a), 502(f)(1) and (2), and 502(j), and may be a new drug without approval in violation of section 505 of the Federal Food, Drug, and Cosmetic Act. Any such preparation

shipped within the jurisdiction of the Act after January 5, 1973 will be the subject of regulatory action.

(2) The Food and Drug Administration withdraws the opinion expressed in trade correspondence TC–412 (issued Feb. 11, 1944) and will regard as adulterated within the meaning of section 601(a) of the Act any cosmetic containing mercury unless the cosmetic meets the conditions of paragraph (d)(2) (i) or (ii) of this section.

(i) It is a cosmetic containing no more than a trace amount of mercury and such trace amount is unavoidable under conditions of good manufacturing practice and is less than 1 part per million (0.0001 percent), calculated as the metal; or

(ii) It is a cosmetic intended for use only in the area of the eye, it contains no more than 65 parts per million (0.0065 percent) of mercury, calculated as the metal, as a preservative, and there is no effective and safe nonmercurial substitute preservative available for use in such cosmetic.

§ 700.14 Use of vinyl chloride as an ingredient, including propellant of cosmetic aerosol products.

(a) Vinyl chloride has been used as an ingredient in cosmetic aerosol products including hair sprays. Where such aerosol products are used in the confines of a small room, as is often the case, the level of vinyl chloride to which the individual may be exposed could be significantly in excess of the safe level established in connection with occupational exposure. Evidence indicates that vinyl chloride inhalation can result in acute toxicity, manifested by dizziness, headache, disorientation, and unconsciousness where inhaled at high concentrations. Studies also demonstrate carcinogenic effects in animals as a result of inhalation exposure to vinyl chloride. Furthermore, vinyl chloride has recently been linked to liver disease, including liver cancer, in workers engaged in the polymerization of vinyl chloride. It is the view of the Commissioner that vinyl chloride is a deleterious substance which may render any cosmetic aerosol product that contains it as an ingredient injurious to users. Accordingly, any cosmetic aerosol product containing vinyl chloride as an ingredient is deemed to be adulterated under section 601(a) of the Federal Food, Drug, and Cosmetic Act.

(b) Any cosmetic aerosol product containing vinyl chloride as an ingredient shipped within the jurisdiction of the Act is subject to regulatory action.

[39 FR 30830, Aug. 26, 1974]

§ 700.15 Use of certain halogenated salicylanilides as ingredients in cosmetic products.

(a) Halogenated salicylanilides (tribromsalan (TBS,3,4′,5–tribromosalicylanilide), dibromsalan (DBS,4′5–dibromosalicylanilide), metabromsalan (MBS, 3,5 –dibromosalicylanilide) and 3,3′,4,5′–tetrachlorosalicylanilide (TCSA)) have been used as antimicrobial agents for a variety of purposes in cosmetic products. These halogenated salicylanilides are potent photosensitizers and cross-sensitizers and can cause disabling skin disorders. In some instances, the photosensitization may persist for prolonged periods as a severe reaction without further exposure to these chemicals. Safer alternative antimicrobial agents are available.

(b) These halogenated salicylanilides are deleterious substances which render any cosmetic that contains them injurious to users. Therefore, any cosmetic product that contains such a halogenated salicylanilide as an ingredient at any level for any purpose is deemed to be adulterated under section 601(a) of the Federal Food, Drug, and Cosmetic Act.

(c) Any cosmetic product containing these halogenated salicylanilides as an ingredient that is initially introduced into interstate commerce after December 1, 1975, that is not in compliance with this section is subject to regulatory action.

[40 FR 50531, Oct. 30, 1975]

§ 700.16 Use of aerosol cosmetic products containing zirconium.

(a) Zirconium–containing complexes have been used as an ingredient in cosmetics and/or cosmetics that are also drugs, as, for example, aerosol antiperspirants. Evidence indicates that certain zirconium compounds

have caused human skin granulomas and toxic effects in the lungs and other organs of experimental animals. When used in aerosol form, some zirconium will reach the deep portions of the lungs of users. The lung is an organ, like skin, subject to the development of granulomas. Unlike the skin, the lung will not reveal the presence of granulomatous changes until they have become advanced and, in some cases, permanent. It is the view of the Commissioner that zirconium is a deleterious substance that may render any cosmetic aerosol product that contains it injurious to users.

(b) Any aerosol cosmetic product containing zirconium is deemed to be adulterated under section 601(a) of the Federal Food, Drug, and Cosmetic Act.

(c) Any such cosmetic product introduced in interstate commerce after September 15, 1977 is subject to regulatory action.

[42 FR 41376, Aug. 16, 1977]

§ 700.18 Use of chloroform as an ingredient in cosmetic products.

(a) Chloroform has been used as an ingredient in cosmetic products. Recent information has become available associating chloroform with carcinogenic effects in animals. Studies conducted by the National Cancer Institute have demonstrated that the oral administration of chloroform to mice and rats induced hepatocellular carcinomas (liver cancer) in mice and renal tumors in male rats. Scientific literature indicates that chloroform is absorbed from the gastrointestinal tract, through the respiratory system, and through the skin. The Commissioner concludes that, on the basis of these findings, chloroform is a deleterious substance which may render injurious to users any cosmetic product that contains chloroform as an ingredient.

(b) Any cosmetic product containing chloroform as an ingredient is adulterated and is subject to regulatory action under sections 301 and 601(a) of the Federal Food, Drug, and Cosmetic Act. Any cosmetic product containing chloroform in residual amounts from its use as a processing solvent during manufacture, or as a byproduct from the synthesis of an ingredient, is not, for the purpose of this section, considered to contain chloroform as an ingredient.

[41 FR 26845, June 29, 1976]

§ 700.19 Use of methylene chloride as an ingredient of cosmetic products.

(a) Methylene chloride has been used as an ingredient of aerosol cosmetic products, principally hair sprays, at concentrations generally ranging from 10 to 25 percent. In a 2-year animal inhalation study sponsored by the National Toxicology Program, methylene chloride produced a significant increase in benign and malignant tumors of the lung and liver of male and female mice. Based on these findings and on estimates of human exposure from the customary use of hair sprays, the Food and Drug Administration concludes that the use of methylene chloride in cosmetic products poses a significant cancer risk to consumers, and that the use of this ingredient in cosmetic products may render these products injurious to health.

(b) Any cosmetic product that contains methylene chloride as an ingredient is deemed adulterated and is subject to regulatory action under sections 301 and 601(a) of the Federal Food, Drug, and Cosmetic Act.

[54 FR 27342, June 29, 1989]

§ 700.23 Chlorofluorocarbon propellants.

The use of chlorofluorocarbons in cosmetics as propellants in self-pressurized containers is prohibited as provided in § 2.125 of this chapter.

[43 FR 11317, Mar. 17, 1978]

§ 700.25 Tamper-resistant packaging requirements for cosmetic products.

(a) *General.* Because most cosmetic liquid oral hygiene products and vaginal products are not now packaged in tamper-resistant retail packages, there is the opportunity for the malicious adulteration of those cosmetic products with health risks to individuals who unknowingly purchase adulterated products and with loss of consumer confidence in the security of cosmetic product packages. The Food and Drug Administration has the authority and responsibility under the Federal Food,

Drug, and Cosmetic Act (the act) to establish a uniform national requirement for tamper-resistant packaging of cosmetic liquid oral hygiene products or products used vaginally that will improve the packaging security and help assure the safety of those products. Such a cosmetic product for retail sale that is not packaged in a tamper-resistant package or that is not properly labeled under this section is adulterated under section 601 of the act or misbranded under section 602 of the act, or both.

(b) *Requirement for tamper-resistant package.* Each manufacturer and packer who packages a cosmetic liquid oral hygiene product or vaginal product for retail sale shall package the product in a tamper-resistant package, if this product is accessible to the public while held for sale. A tamper-resistant package is one having an indicator or barrier to entry which, if breached or missing, can reasonably be expected to provide visible evidence to consumers that tampering has occurred. To reduce the likelihood of substitution of a tamper-resistant feature after tampering, the indicator or barrier to entry is required to be distinctive by design (e.g., an aerosol product container) or by the use of an identifying characteristic (e.g., a pattern, name, registered trademark, logo, or picture). For purposes of this section, the term ''distinctive by design'' means the packaging cannot be duplicated with commonly available materials or through commonly available processes. For purposes of this section, the term ''aerosol product'' means a product which depends upon the power of a liquified or compressed gas to expel the contents from the container. A tamper-resistant package may involve an immediate-container and closure system or secondary-container or carton system or any combination of systems intended to provide a visual indication of package integrity. The tamper-resistant feature shall be designed to and shall remain intact when handled in a reasonable manner during manufacture, distribution, and retail display.

(c) *Labeling.* Each retail package of a cosmetic product covered by this section, except aerosol products as defined in paragraph (b) of this section, is required to bear a statement that is prominently placed so that consumers are alerted to the specific tamper-resistant feature of the package. The labeling statement is also required to be so placed that it will be unaffected if the tamper-resistant feature of the package is breached or missing. If the tamper-resistant feature chosen to meet the requirement in paragraph (b) of this section is one that uses an identifying characteristic, that characteristic is required to be referred to in the labeling statement. For example, the labeling statement on a bottle with a shrink band could say ''For your protection, this bottle has an imprinted seal around the neck.''

(d) *Requests for exemptions from packaging and labeling requirements.* A manufacturer or packer may request an exemption from the packaging and labeling requirements of this section. A request for an exemption is required to be submitted in the form of a citizen petition under § 10.30 of this chapter and should be clearly identified on the envelope as a ''Request for Exemption from Tamper-resistant Rule.'' The petition is required to contain the following:

(1) The name of the product.

(2) The reasons that the product's compliance with the tamper-resistant packaging or labeling requirements of this section is unnecessary or cannot be achieved.

(3) A description of alternative steps that are available, or that the petitioner has already taken, to reduce the likelihood that the product will be the subject of malicious adulteration.

(4) Other information justifying an exemption.

This information collection requirement has been approved by the Office of Management and Budget under number 0910–0149.

(e) *Effective date.* Cosmetic products covered by this section are required to comply with the requirements of this section on the dates listed below except to the extent that a product's manufacturer or packer has obtained an exemption from a packaging or labeling requirement.

(1) *Initial effective date for packaging requirements.* (i) The packaging requirement in paragraph (b) of this section is

effective on Feburary 7, 1983 for each affected cosmetic product (except vaginal tablets) packaged for retail sale on or after that date, except for the requirement in paragraph (b) of this section for a distinctive indicator or barrier to entry.

(ii) The packaging requirement in paragraph (b) of this section is effective on May 5, 1983 for each cosmetic product that is a vaginal tablet packaged for retail sale on or after that date.

(2) *Initial effective date for labeling requirements.* The requirement in paragraph (b) of this section that the indicator or barrier to entry be distinctive by design and the requirement in paragraph (c) of this section for a labeling statement are effective on May 5, 1983 for each affected cosmetic product packaged for retail sale on or after that date, except that the requirement for a specific label reference to any identifying characteristic is effective on February 6, 1984 for each affected cosmetic product packaged for retail sale on or after that date.

(3) *Retail level effective date.* The tamper-resistant packaging requirement of paragraph (b) of this section is effective February 6, 1984 for each affected cosmetic product held for sale on or after that date that was packaged for retail sale before May 5, 1983. This does not include the requirement in paragraph (b) of this section that the indicator or barrier to entry be distinctive by design. Products packaged for retail sale after May 5, 1983, as required to be in compliance with all aspects of the regulations without regard to the retail level effective date.

[47 FR 50451, Nov. 5, 1982; 48 FR 1707, Jan. 14, 1983; 48 FR 11427, Mar. 18, 1983, as amended at 48 FR 16664, Apr. 19, 1983; 48 FR 37624, Aug. 19, 1983]

EFFECTIVE DATE NOTE: See 48 FR 41579, Sept. 16, 1983, for a document announcing an interim stay of the effective date of certain provisions in paragraph (e)(3) of § 700.25.

PART 701—COSMETIC LABELING

Subpart A—General Provisions

Subpart B—Package Form

Subpart C—Labeling of Specific Ingredients

AUTHORITY: Secs. 201, 502, 601, 602, 603, 701, 704 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, 352, 361, 362, 363, 371, 374); secs. 5, 6 of the Fair Packaging and Labeling Act (15 U.S.C. 1454, 1455).

SOURCE: 39 FR 10056, Mar. 15, 1974, unless otherwise noted.

Subpart A—General Provisions

§ 701.1 Misbranding.

(a) Among representations in labeling of a cosmetic which render such cosmetic misbranded is a false or misleading representation with respect to another cosmetic or a food, drug, or device.

(b) The labeling of a cosmetic which contains two or more ingredients may be misleading by reason (among other reasons) of the designation of such cosmetic in such labeling by a name which includes or suggests the name of one or more but not all such ingredients, even though the names of all such ingredients are stated elsewhere in the labeling.

§ 701.2 Form of stating labeling requirements.

(a) A word, statement, or other information required by or under authority of the Act to appear on the label may lack that prominence and conspicuousness required by section 602(c) of the Act by reason (among other reasons) of:

(1) The failure of such word, statement, or information to appear on the part or panel of the label which is

presented or displayed under customary conditions of purchase;

(2) The failure of such word, statement, or information to appear on two or more parts or panels of the label, each of which has sufficient space therefor, and each of which is so designed as to render it likely to be, under customary conditions of purchase, the part or panel displayed;

(3) The failure of the label to extend over the area of the container or package available for such extension, so as to provide sufficient label space for the prominent placing of such word, statement, or information;

(4) Insufficiency of label space (for the prominent placing of such word, statement, or information) resulting from the use of label space for any word, statement, design, or device which is not required by or under authority of the Act to appear on the label;

(5) Insufficiency of label space (for the prominent placing of such word, statement, or information) resulting from the use of label space to give materially greater conspicuousness to any other word, statement, or information, or to any design or device;

(6) Smallness or style of type in which such word, statement, or information appears, insufficient background contrast, obscuring designs or vignettes, or crowding with other written, printed, or graphic matter.

(b)(1) All words, statements, and other information required by or under authority of the Act to appear on the label or labeling shall appear thereon in the English language: *Provided, however,* That in the case of articles distributed solely in the Commonwealth of Puerto Rico or in a Territory where the predominant language is one other than English, the predominant language may be substituted for English.

(2) If the label contains any representation in a foreign language, all words, statements, and other information required by or under authority of the Act to appear on the label shall appear thereon in the foreign language.

(3) If the labeling contains any representation in a foreign language, all words, statements, and other information required by or under authority of the Act to appear on the label or labeling shall appear on the labeling in the foreign language.

§ 701.3 Designation of ingredients.

(a) The label on each package of a cosmetic shall bear a declaration of the name of each ingredient in descending order of predominance, except that fragrance or flavor may be listed as fragrance or flavor. An ingredient which is both fragrance and flavor shall be designated by each of the functions it performs unless such ingredient is identified by name. No ingredient may be designated as fragrance or flavor unless it is within the meaning of such term as commonly understood by consumers. Where one or more ingredients is accepted by the Food and Drug Administration as exempt from public disclosure pursuant to the procedure established in § 720.8(a) of this chapter, in lieu of label declaration of identity the phrase ''and other ingredients'' may be used at the end of the ingredient declaration.

(b) The declaration of ingredients shall appear with such prominence and conspicuousness as to render it likely to be read and understood by ordinary individuals under normal conditions of purchase. The declaration shall appear on any appropriate information panel in letters not less than 1/16 of an inch in height and without obscuring design, vignettes, or crowding. In the absence of sufficient space for such declaration on the package, or where the manufacturer or distributor wishes to use a decorative container, the declaration may appear on a firmly affixed tag, tape, or card. In those cases where there is insufficient space for such declaration on the package, and it is not practical to firmly affix a tag, tape, or card, the Commissioner may establish by regulation an acceptable alternate, e.g., a smaller type size. A petition requesting such a regulation as an amendment to this paragraph shall be submitted pursuant to part 10 of this chapter.

(c) A cosmetic ingredient shall be identified in the declaration of ingredients by:

(1) The name specified in § 701.30 as established by the Commissioner for that ingredient for the purpose of

cosmetic ingredient labeling pursuant to paragraph (e) of this section;

(2) In the absence of the name specified in § 701.30, the name adopted for that ingredient in the following editions and supplements of the following compendia, listed in order as the source to be utilized:

(i) CTFA (Cosmetic, Toiletry and Fragrance Association, Inc.) Cosmetic Ingredient Dictionary, Second Ed., 1977 (available from the Cosmetic, Toiletry and Fragrance Association, Inc. 1110 Vermont Ave. NW., Suite 800, Washington, DC 20005, or available for inspection at the Office of the Federal Register, 800 North Capitol Street, NW., suite 700, Washington, DC 20408), which is incorporated by reference, except for the following deletions and revisions:

(*a*) The following names are not adopted for the purpose of cosmetic ingredient labeling:

Acid Black 58
Acid Black 107
Acid Black 139
Acid Blue 168
Acid Blue 170
Acid Blue 188
Acid Blue 209
Acid Brown 19
Acid Brown 30
Acid Brown 44
Acid Brown 45
Acid Brown 46
Acid Brown 48
Acid Brown 224
Acid Orange 80
Acid Orange 85
Acid Orange 86
Acid Orange 88
Acid Orange 89
Acid Orange 116
Acid Red 131
Acid Red 213
Acid Red 252
Acid Red 259
Acid Violet 73
Acid Violet 76
Acid Violet 99
Acid Yellow 114
Acid Yellow 127
Direct Yellow 81
Solvent Black 5
Solvent Brown 43
Solvent Yellow 63
Solvent Yellow 90

(*b*) The following names are adopted for the purpose of cosmetic ingredient labeling, provided the respective monographs are revised to describe their otherwise disclosed chemical compositions, or describe their chemical compositions more precisely, and such revised monographs are published in supplements to this dictionary edition by July 18, 1980.

Acid Black 2
Benzophenone-11
Carbomer 934
Carbomer 934P
Carbomer 940
Carbomer 941
Carbomer 960
Carbomer 961
Chlorofluorocarbon 11S
Dimethicone Copolyol
Disperse Red 17
Pigment Green 7
Polyamino Sugar Condensate
SD Alcohol (all 27 alphanumeric designations)
Sodium Chondroitin Sulfate
Synthetic Beeswax

(*c*) The following names are adopted for the purpose of cosmetic ingredient labeling until January 19, 1981.

Amphoteric (all 20 numeric designations)
Quaternium (all 49 numeric designations)

(ii) United States Pharmacopeia, 19th Ed., 1975, and Second Supplement to the USP XIX and NF XIV, 1976. (Copies are available from the U.S. Pharmacopeial Convention, Inc., 12601 Twinbrook Parkway, Rockville, MD 20852, or available for inspection at the Office of the Federal Register, 800 North Capitol Street, NW., suite 700, Washington, DC 20408.)

(iii) National Formulary, 14th Ed., 1975, and Second Supplement to the USP XIX and NF XIV, 1976. (Copies are available from the U.S. Pharmacopeial Convention, Inc., 12601 Twinbrook Parkway, Rockville, MD 20852, or available for inspection at the Office of the Federal Register, 800 North Capitol Street, NW., suite 700, Washington, DC 20408).

(iv) Food Chemicals Codex, 2d Ed., 1972; First Supplement, 1974, and Second Supplement, 1975, which are incorporated by reference. Copies are available from the Center for Food Safety and Applied Nutrition, Food and Drug Administration, 200 C St. SW., Washington, DC 20204, or available for inspection at the Office of the Federal Register, 800 North Capitol Street, NW., suite 700, Washington, DC 20408.

(v) USAN and the USP dictionary of drug names, USAN 1975, 1961–1975

cumulative list. (Copies are available from the U.S. Pharmacopeial Convention, Inc., 12601 Twinbrook Parkway, Rockville, MD 20852, or available for inspection at the Office of the Federal Register, 800 North Capitol Street, NW., suite 700, Washington, DC 20408.)

(3) In the absence of such a listing, the name generally recognized by consumers.

(4) In the absence of any of the above, the chemical or other technical name or description.

(d) Where a cosmetic product is also a drug, the declaration shall first declare the active drug ingredients as required under section 502(e) of the Federal Food, Drug, and Cosmetic Act, and shall then declare the cosmetic ingredients.

(e) Interested persons may submit a petition requesting the establishment of a specific name for a cosmetic ingredient pursuant to part 10 of this chapter. The Commissioner may also propose such a name on his own initiative.

(f) As an alternative to listing all ingredients in descending order of predominance, ingredients may be grouped and the groups listed in the following manner and order:

(1) Ingredients, other than color additives, present at a concentration greater than 1 percent, in descending order of predominance; followed by

(2) Ingredients, other than color additives, present at a concentration of not more than 1 percent, without respect to order of predominance; followed by

(3) Color additives, without respect to order of predominance. Ingredients specified in paragraph (f)(2) of this section may be included with those specified in paragraph (f)(1) of this section and listed in descending order of predominance.

(g) A declaration of ingredients may include an ingredient not in the product if the ingredient is identified by the phrase ''may contain'' and:

(1) It is a color additive added to some batches of the product for purposes of color matching; or

(2)(i) The same declaration of ingredients is also used for other products similar in composition and intended for the same use, including products which may be assortments of products similar in composition and intended for the same use; and

(ii) Such products are ''shaded'' products, i.e., those falling within the product categories identified in § 720.4 (c)(3), (7) and (8)(v) of this chapter; and

(iii) All products sharing the common declaration of ingredients are sold by the labeler under a common trade name or brand designation, and no trade name or brand designation not common to all such products appears in the labeling of any of them; and

(iv) The ingredient is a color additive.

(h) As an alternative to a declaration of color additive ingredients for each product, the color additives of an assortment of cosmetic products that are sold together in the same package may be declared in a single composite list in a manner that is not misleading and that indicates that the list pertains to all the products.

(i) As an alternative to the declaration of ingredients specified in paragraph (b) of this section, the declaration of ingredients may appear in letters not less than 1/16 of an inch in height in labeling accompanying the product, as for example, on padded sheets or in leaflets, if the total surface area of the package is less than 12 square inches. This paragraph is inapplicable to any packaged cosmetic product enclosed in an outer container, e.g., a folding carton. In addition, this paragraph is applicable only to cosmetic products meeting one of the following requirements:

(1) The cosmetic products are held and displayed for sale in tightly compartmented trays or racks of a display unit. The holder of the labeling bearing the declaration of ingredients shall be attached to the display unit; or

(2) The cosmetic products are ''shaded'' products, i.e., those falling within the product categories identified in § 720.4 (c)(3), (7) and (8)(v) of this chapter, and are held for sale in tightly compartmented trays or racks. The holder of the labeling bearing the declaration of ingredients shall be attached to a display chart bearing samples of the product shades, which is displayed to purchasers. Such a display chart shall be of such construction and design as to permit its continuous use

as a display, such as on a counter, and shall be designed for the primary purpose of displaying samples of the shades of the products.

(j) The holder of labeling bearing a declaration of ingredients and used in accordance with paragraph (i) of this section shall be attached to the display unit or chart and shall meet one of the following conditions:

(1) The labeling is on the front of the display unit or chart and can be read in full by a purchaser facing the display unit or chart under customary conditions of retail sale; or

(2) The labeling is on the front of the display unit or chart, is partially visible, and is accompanied by a conspicuous notice on the front of the display unit or chart describing the location of such labeling in letters not less than 3⁄16 of an inch in height, e.g., ''Ingredient lists above'', that can be read by a purchaser facing the display unit or chart under customary conditions of retail sale, or by the notice required by provisions in paragraph (k)(3) of this section, if conspicuous at all times; or

(3) The labeling is on a side of the display unit or chart, but not on the top, back, or bottom, and is accompanied by a conspicuous notice on the front of the display unit or chart describing the location of such labeling in letters not less than 3⁄16 of an inch in height, e.g., ''Ingredient lists located on right side of display'', that can be read by a purchaser facing the display unit or chart under customary conditions of retail sale.

(k) Any use of a display unit or chart bearing labeling under the provisions of paragraph (i) of this section shall meet the following requirements:

(1) All articles of labeling bearing ingredient declarations and used in conjunction with any one display unit or chart shall be identical and shall declare the ingredients of all products sold in conjunction with the display unit or chart for which the ingredient declaration is made pursuant to paragraph (i) of this section.

(2) Any display unit or chart intended for such use shall be shipped together with the labeling intended to be attached to it.

(3) Every display unit or chart and/or labeling system shall be designed so that the words ''Federal law requires ingredient lists to be displayed here'' in letters not less than 3⁄16 of an inch in height (i) become conspicuous when no ingredient declarations are displayed and when the last list has been taken, or (ii) are conspicuous at all times adjacent to the place where ingredient declarations are to be attached.

(4) Any labeling containing a declaration of ingredients which reflects a formulation change and not shipped accompanying a display unit or chart shall be dated. Whenever any formulation change is made, and the labeling containing the declaration of ingredients is thereby required to be used in conjunction with products of both the old and new formulations, the labeling shall declare the ingredients of both the old and new formulations separately in a way that is not misleading and in a way that permits the purchaser to identify the ingredient declaration applicable to each package, or which clearly advises the purchaser that the formulation has been changed and that either declaration may be applicable.

(5) Sufficient copies of the declaration of ingredients shall be provided with each shipment of a cosmetic so that a purchaser may obtain a copy of the declaration with each purchase. Display units and replacement labeling for display units shall be accompanied by instructions to the retailer, which when followed will result in compliance with the requirements of this section. Copies of the declaration accompanying refills shall be attached to the specific refill items to which they pertain, or shall be packed with the specific refill items to which they pertain, in a container that does not contain other cosmetic products.

(6) The firm whose name appears on a product pursuant to § 701.12 shall promptly mail a copy of the declaration of ingredients to any person requesting it.

(7) The display unit or chart shall be designed and located such that the labeling is easily accessible to a purchaser facing the display unit or chart under customary conditions of retail sale.

(l) The provisions of this section do not require the declaration of

incidental ingredients that are present in a cosmetic at insignificant levels and that have no technical or functional effect in the cosmetic. For the purpose of this paragraph, incidental ingredients are:

(1) Substances that have no technical or functional effect in the cosmetic but are present by reason of having been incorporated into the cosmetic as an ingredient of another cosmetic ingredient.

(2) Processing aids, which are as follows:

(i) Substances that are added to a cosmetic during the processing of such cosmetic but are removed from the cosmetic in accordance with good manufacturing practices before it is packaged in its finished form.

(ii) Substances that are added to a cosmetic during processing for their technical or functional effect in the processing, are converted to substances the same as constituents of declared ingredients, and do not significantly increase the concentration of those constituents.

(iii) Substances that are added to a cosmetic during the processing of such cosmetic for their technical and functional effect in the processing but are present in the finished cosmetic at insignificant levels and do not have any technical or functional effect in that cosmetic.

(m) In the event that there is a current or anticipated shortage of a cosmetic ingredient, the declaration required by this section may specify alternatives to any ingredients that may be affected. An alternative ingredient shall be declared either (1) immediately following the normally used ingredient for which it substitutes, in which case it shall be identified as an alternative ingredient by the word ''or'' following the name of the normally used ingredient and any other alternative ingredient, or (2) following the declaration of all normally used ingredients, in which case the alternative ingredients in the group so listed shall be listed in expected descending order of predominance or in accordance with the provisions of paragraph (f) of this section and shall be identified as alternative ingredients by the phrase ''may also contain''. This paragraph is inapplicable to any ingredient mentioned in advertising, or in labeling other than in the declaration of ingredients required by this section.

(n) In the event that the shortage of a cosmetic ingredient necessitates a formulation change, packages bearing labels declaring the ingredients of the old formulation may be used if the revised ingredient declaration appears (1) on a firmly affixed tag, tape, card, or sticker or similar overlabeling attached to the package and bearing the conspicuous words ''new ingredient list'' in letters not less than 1/16 of an inch in height, or (2) on labeling inside an unsealed package and the package bears the conspicuous words, on a sticker or similar overlabeling, ''new ingredient list inside'' in letters not less than 1/16 of an inch in height.

(o) The ingredients of products that are similar in composition and intended for the same use may be declared as follows:

(1) The declaration of ingredients for an assortment of such products that are sold together in the same package, e.g., eyeshadows of different colors, may declare the ingredients that are common to all the products, in a single list in their cumulative order of predominance or in accordance with the provisions of paragraph (f) of this section, together with a statement, in terms that are as informative as practicable and that are not misleading, declaring the other ingredients and identifying the products in which they are present. The color additive ingredients of all the products in such an assortment, whether or not common to all the products, may be declared in a single composite list following the declaration of the other ingredients without identifying the products in which they are present.

(2) The ingredients of an assortment of such products that are sold together in the same package, e.g., eyeshadows of different colors, may be declared in a single list in their cumulative order of predominance or in accordance with the provisions of paragraph (f) of this section, if the package is designed such that it has a total surface area available to bear labeling of less than 12 square inches. For the purpose of this paragraph, surface area is not available

for labeling if physical characteristics of the package surface, e.g., decorative relief, make application of a label impractical.

(3) The declaration of ingredients for such a product that is individually packaged and bears a label that is shared with other products pursuant to the provisions of paragraph (g)(2) of this section, e.g., one lipstick in a line of lipsticks, may declare the ingredients that are common to all such products, in a single list in their cumulative order of predominance or in accordance with the provisions of paragraph (f) of this section, together with a statement, in terms that are as informative as practicable and that are not misleading, declaring the other ingredients in such products, and identifying the products in which they are present. The color additive ingredients shall be declared in accordance with the provisions of paragraph (g) of this section.

(4) The declaration of ingredients for an assortment of such cosmetic products that bears a label that is shared with other products pursuant to the provisions of paragraph (g)(2) of this section, e.g., one of several compacts in a line of compacts, may declare the ingredients that are common to all such products, in a single list in their cumulative order of predominance or in accordance with the provisions of paragraph (f) of this section, together with a statement, in terms that are as informative as practicable and that are not misleading, declaring the other ingredients in such products and identifying the products in which they are present. The color additive ingredients shall be declared in accordance with the provisions of paragraph (g) of this section.

(p) As an alternative to the declaration of ingredients in letters not less than 1/16 of an inch in height, letters may be not less than 1/32 of an inch in height if the package is designed such that it has a total surface area available to bear labeling of less than 12 square inches. For the purpose of this paragraph, surface area is not available for labeling if physical characteristics of the package surface, e.g., decorative relief, make application of a label impractical.

(q) The inside containers in a multiunit or multicomponent retail cosmetic package are not required to bear a declaration of ingredients when the labeling of the multiunit or multicomponent retail cosmetic package meets all the requirements of this section and the inside containers are not intended to be, and are not customarily, separated from the retail package for retail sale.

(r) In the case of cosmetics distributed to the consumers by direct mail, as an alternative to the declaration of ingredients on an information panel, the declaration of ingredients may appear in letters not less than 1/16 of an inch in height in labeling that accompanies and specifically relates to the cosmetic(s) mailed, or in labeling furnished to each consumer for his personal use and from which he orders cosmetics through the mail, e.g., a direct mail sales catalog or brochure, provided all of the following additional requirements are met:

(1) The declarations of ingredients are conspicuous and presented in a way that permits the consumer to identify the declaration of ingredients applicable to each cosmetic.

(2) The package mailed to the consumer is accompanied by a notice located on, or affixed to, the top of the package or on top of the contents inside the package, or on the face of the package platform surrounding and holding the product(s), readily visible to the consumer on opening of the package, and provides the following information in letters not less than 3/16 of an inch in height:

(i) The location of the declarations of ingredients, e.g., in an accompanying brochure, or in a sales catalog used for ordering;

(ii) A statement that a copy of the declaration of ingredients will be mailed promptly to any person requesting it; and

(iii) The name and place of business of the mail order distributor,

(3) The mail order distributor promptly mails a copy of the

declaration of ingredients to any person requesting it.

[39 FR 10056, Mar. 15, 1974, as amended at 40 FR 8922, Mar. 3, 1975; 40 FR 18426, Apr. 28, 1975; 42 FR 4718, Jan. 25, 1977; 42 FR 15676, Mar. 22, 1977; 42 FR 24255, May 31, 1977; 42 FR 46516, Sept. 16, 1977; 42 FR 61257, Dec. 2, 1977; 45 FR 3577, Jan. 18, 1980; 47 FR 9397, Mar. 5, 1982; 54 FR 24900, June 12, 1989]

§ 701.9 Exemptions from labeling requirements.

(a) Except as provided by paragraphs (b) and (c) of this section, a shipment or other delivery of a cosmetic which is, in accordance with the practice of the trade, to be processed, labeled, or repacked in substantial quantity at an establishment other than that where originally processed or packed, shall be exempt, during the time of introduction into and movement in interstate commerce and the time of holding in such establishment, from compliance with the labeling requirements of sections 601(a) and 602(b) of the act if:

(1) The person who introduced such shipment or delivery into interstate commerce is the operator of the establishment where such cosmetic is to be processed, labeled, or repacked; or

(2) In case such person is not such operator, such shipment or delivery is made to such establishment under a written agreement, signed by and containing the post office addresses of such person and such operator, and containing such specifications for the processing, labeling, or repacking, as the case may be, of such cosmetic in such establishment as will insure, if such specifications are followed, that such cosmetic will not be adulterated or misbranded within the meaning of the act upon completion of such processing, labeling, or repacking. Such person and such operator shall each keep a copy of such agreement until 2 years after the final shipment or delivery of such cosmetic from such establishment, and shall make such copies available for inspection at any reasonable hour to any officer or employee of the Department who requests them.

(b) An exemption of a shipment or other delivery of a cosmetic under paragraph (a)(1) of this section shall, at the beginning of the act of removing such shipment or delivery, or any part thereof, from such establishment, become void ab initio if the cosmetic comprising such shipment, delivery, or part is adulterated or misbranded within the meaning of the act when so removed.

(c) An exemption of a shipment or other delivery of a cosmetic under paragraph (a)(2) of this section shall become void ab initio with respect to the person who introduced such shipment or delivery into interstate commerce upon refusal by such person to make available for inspection a copy of the agreement, as required by such clause.

(d) An exemption of a shipment or other delivery of a cosmetic under paragraph (a)(2) of this section shall expire:

(1) At the beginning of the act of removing such shipment or delivery, or any part thereof, from such establishment if the cosmetic comprising such shipment, delivery, or part is adulterated or misbranded within the meaning of the act when so removed; or

(2) Upon refusal by the operator of the establishment where such cosmetic is to be processed, labeled, or repacked, to make available for inspection a copy of the agreement, as required by such clause.

Subpart B—Package Form

§ 701.10 Principal display panel.

The term *principal display panel* as it applies to cosmetics in package form and as used in this part, means the part of a label that is most likely to be displayed, presented, shown, or examined under customary conditions of display for retail sale. The principal display panel shall be large enough to accommodate all the mandatory label information required to be placed thereon by this part with clarity and conspicuousness and without obscuring designs, vignettes, or crowding. Where packages bear alternate principal display panels, information required to be placed on the principal display panel shall be duplicated on each principal display panel. For the purpose of obtaining uniform type size in declaring the quantity of contents of all packages of substantially the same size, the term ''area of the principal display panel''

means the area of the side or surface that bears the principal display panel, which area shall be:

(a) In the case of a rectangular package where one entire side properly can be considered to be the principal display panel side, the product of the height times the width of that side;

(b) In the case of a cylindrical or nearly cylindrical container, 40 percent of the product of the height of the container times the circumference; and

(c) In the case of any other shape of container, 40 percent of the total surface of the container: *Provided, however,* That where such container presents an obvious ''principal display panel'' such as the top of a triangular or circular package, the area shall consist of the entire top surface.

In determining the area of the principal display panel, exclude tops, bottoms, flanges at the tops and bottoms of cans, and shoulders and necks of bottles or jars. In the case of cylindrical or nearly cylindrical containers, information required by this part to appear on the principal display panel shall appear within that 40 percent of the circumference which is most likely to be displayed, presented, shown, or examined under customary conditions of display for retail sale.

§ 701.11 Identity labeling.

(a) The principal display panel of a cosmetic in package form shall bear as one of its principal features a statement of the identity of the commodity.

(b) Such statement of identity shall be in terms of:

(1) The common or usual name of the cosmetic; or

(2) An appropriately descriptive name or, when the nature of the cosmetic is obvious, a fanciful name understood by the public to identify such cosmetic; or

(3) An appropriate illustration or vignette representing the intended cosmetic use.

(c) The statement of identity shall be presented in bold type on the principal display panel, shall be in a size reasonably related to the most prominent printed matter on such panel, and shall be in lines generally parallel to the base on which the package rests as it is designed to be displayed.

§ 701.12 Name and place of business of manufacturer, packer, or distributor.

(a) The label of a cosmetic in package form shall specify conspicuously the name and place of business of the manufacturer, packer, or distributor.

(b) The requirement for declaration of the name of the manufacturer, packer, or distributor shall be deemed to be satisfied in the case of a corporation only by the actual corporate name, which may be preceded or followed by the name of the particular division of the corporation. Abbreviations for ''Company,'' ''Incorporated,'' etc., may be used and ''The'' may be omitted. In the case of an individual, partnership, or association, the name under which the business is conducted shall be used.

(c) Where the cosmetic is not manufactured by the person whose name appears on the label, the name shall be qualified by a phrase that reveals the connection such person has with such cosmetic; such as, ''Manufactured for _____'', ''Distributed by _____'', or any other wording that expresses the facts.

(d) The statement of the place of business shall include the street address, city, State, and ZIP Code; however, the street address may be omitted if it is shown in a current city directory or telephone directory. The requirement for inclusion of the ZIP Code shall apply only to consumer commodity labels developed or revised after the effective date of this section. In the case of nonconsumer packages, the ZIP Code shall appear either on the label or the labeling (including the invoice).

(e) If a person manufactures, packs, or distributes a cosmetic at a place other than his principal place of business, the label may state the principal place of business in lieu of the actual place where such cosmetic was manufactured or packed or is to be distributed, unless such statement would be misleading.

§ 701.13 Declaration of net quantity of contents.

(a) The label of a cosmetic in package form shall bear a declaration of the net quantity of contents. This shall be expressed in terms of weight, measure,

numerical count, or a combination of numerical count and weight or measure. The statement shall be in terms of fluid measure if the cosmetic is liquid or in terms of weight if the cosmetic is solid, semisolid, or viscous, or a mixture of solid and liquid. If there is a firmly established, general consumer usage and trade custom of declaring the net quantity of a cosmetic by numerical count, linear measure, or measure of area, such respective term may be used. If there is a firmly established, general consumer usage and trade custom of declaring the contents of a liquid cosmetic by weight, or a solid, semisolid, or viscous cosmetic by fluid measure, it may be used. Whenever the Commissioner determines for a specific packaged cosmetic that an existing practice of declaring net quantity of contents by weight, measure, numerical count, or a combination of these does not facilitate value comparisons by consumers, he shall by regulation designate the appropriate term or terms to be used for such cosmetic.

(b) Statements of weight shall be in terms of avoirdupois pound and ounce. Statements of fluid measure shall be in terms of the U.S. gallon of 231 cubic inches and quart, pint, and fluid-ounce subdivisions thereof and shall express the volume at 68° F. (20° C.).

(c) When the declaration of quantity of contents by numerical count, linear measure, or measure of area does not give accurate information as to the quantity of cosmetic in the package, it shall be augmented by such statement of weight, measure, or size of the individual units or the total weight or measure of the cosmetic as will give such information.

(d) The declaration may contain common or decimal fractions. A common fraction shall be in terms of halves, quarters, eighths, sixteenths, or thirty-seconds; except that if there exists a firmly established, general consumer usage and trade custom of employing different common fractions in the net quantity declaration of a particular commodity they may be employed. A common fraction shall be reduced to its lowest terms; a decimal fraction shall not be carried out to more than two places. A statement that includes small fractions of an ounce shall be deemed to permit smaller variations than one which does not include such fractions.

(e) The declaration shall be located on the principal display panel of the label; with respect to packages bearing alternate principal display panels, it shall be duplicated on each principal display panel: *Provided,* That:

(1) The principal display panel of a cosmetic marketed in a ''boudoir-type'' container including decorative cosmetic containers of the ''cartridge,'' ''pill box,'' ''compact,'' or ''pencil'' variety, and those with a capacity of one-fourth ounce or less, may be considered to be a tear-away tag or tape affixed to the decorative container and bearing the mandatory label information as required by this part, but the type size of the net quantity of contents statement shall be governed by the dimensions of the decorative container; and

(2) The principal display panel of a cosmetic marketed on a display card to which the immediate container is affixed may be considered to be the display panel of the card, and the type size of the net quantity of content statement is governed by the dimensions of the display card.

(f) The declaration shall appear as a distinct item on the principal display panel, shall be separated (by at least a space equal to the height of the lettering used in the declaration) from other printed label information appearing above or below the declaration and (by at least a space equal to twice the width of the letter ''N'' of the style of type used in the quantity of contents statement) from other printed label information appearing to the left or right of the declaration. It shall not include any term qualifying a unit of weight, measure, or count (such as ''giant pint'' and ''full quart'') that tends to exaggerate the amount of the cosmetic in the container. It shall be placed on the principal display panel within the bottom 30 percent of the area of the label panel in line generally parallel to the base on which the package rests as it is designed to be displayed: *Provided,* That:

(1) On packages having a principal display panel of 5 square inches or less, the requirement for placement within the bottom 30 percent of the area of the

label panel shall not apply when the declaration of net quantity of contents meets the other requirements of this part; and

(2) In the case of a cosmetic that is marketed with both outer and inner retail containers bearing the mandatory label information required by this part, and the inner container is not intended to be sold separately, the net quantity of contents placement requirement of this section applicable to such inner containers is waived.

(g) The declaration shall accurately reveal the quantity of cosmetic in the package exclusive of wrappers and other material packed therewith: *Provided,* That:

(1) In the case of cosmetics packed in containers designed to deliver the cosmetic under pressure, the declaration shall state the net quantity of the contents that will be expelled when the instructions for use as shown on the container are followed. The propellant is included in the net quantity declaration; and

(2) In the case of a package which contains the integral components making up a complete kit, and which is designed to deliver the components in the manner of an application (for example, a home permanent wave kit), the declaration may state the net quantity of the contents in nondeceptive terms of the number of applications available in the kit when the instructions for use as shown on the container are followed.

(h) The declaration shall appear in conspicuous and easily legible boldface print or type in distinct contrast (by typography, layout, color, embossing, or molding) to other matter on the package; except that a declaration of net quantity blown, embossed, or molded on a glass or plastic surface is permissible when all label information is so formed on the surface. Requirements of conspicuousness and legibility shall include the specifications that:

(1) The ratio of height to width (of the letter) shall not exceed a differential of 3 units to 1 unit (no more than 3 times as high as it is wide).

(2) Letter heights pertain to upper case or capital letters. When upper and lower case or all lower case letters are used, it is the lower case letter ''o'' or its equivalent that shall meet the minimum standards.

(3) When fractions are used, each component numeral shall meet one-half the minimum height standards.

(i) The declaration shall be in letters and numerals in a type size established in relationship to the area of the principal display panel of the package and shall be uniform for all packages of substantially the same size by complying with the following type specifications:

(1) Not less than one-sixteenth inch in height on packages the principal display panel of which has an area of 5 square inches or less.

(2) Not less than one-eighth inch in height on packages the principal display panel of which has an area of more than 5 but not more than 25 square inches.

(3) Not less than three-sixteenths inch in height on packages the principal display panel of which has an area of more than 25 but not more than 100 square inches.

(4) Not less than one-fourth inch in height on packages the principal display panel of which has an area of more than 100 square inches, except not less than one-half inch in height if the area is more than 400 square inches.

Where the declaration is blown, embossed, or molded on a glass or plastic surface rather than by printing, typing, or coloring, the lettering sizes specified in paragraphs (i)(1) through (4) of this section shall be increased by one-sixteenth of an inch.

(j) On packages containing less than 4 pounds or 1 gallon and labeled in terms of weight or fluid measure:

(1) The declaration shall be expressed both in ounces, with identification by weight or by liquid measure and, if applicable (1 pound or 1 pint or more), followed in parentheses by a declaration in pounds for weight units, with any remainder in terms of ounces or common or decimal fractions of the pound (as set forth in paragraphs (m)(1) and (2) of this section), or in the case of liquid measure, in the largest whole units (quarts, quarts and pints, or pints, as appropriate) with any remainder in terms of fluid ounces or common or decimal fractions of the pint or quart (as set forth in paragraphs (m)(3) and

(4) of this section). Net weight or fluid measure of less than 1 ounce shall be expressed in common or decimal fractions of the respective ounce and not in drams.

(2) The declaration may appear in more than one line. The term ''net weight'' shall be used when stating the net quantity of contents in terms of weight. Use of the terms ''net'' or ''net contents'' in terms of fluid measure or numerical count is optional. It is sufficient to distinguish avoirdupois ounce from fluid ounce through association of terms; for example, ''Net wt. 6 oz.'' or ''6 oz. net wt.'' and ''Net contents 6 fl. oz.'' or ''6 fl. oz.''

(k) On packages containing 4 pounds or 1 gallon or more and labeled in terms of weight or fluid measure, the declaration shall be expressed in pounds for weight units with any remainder in terms of ounces or common or decimal fractions of the pound; in the case of fluid measure, it shall be expressed in the largest whole unit (gallons, followed by common or decimal fractions of a gallon or by the next smaller whole unit or units (quarts or quarts and pints)) with any remainder in terms of fluid ounces or common or decimal fractions of the pint or quart (as set forth in paragraph (m)(5) of this section).

(l) [Reserved]

(m) Examples: (1) A declaration of 1½ pounds weight shall be expressed as ''Net wt. 24 oz. (1 lb. 8 oz.)'', ''Net wt. 24 oz. (1½ lb.)'', or ''Net wt. 24 oz. (1.5 lb.)''.

(2) A declaration of three-fourths pound avoirdupois weight shall be expressed as ''Net wt. 12 oz.''

(3) A declaration of 1 quart liquid measure shall be expressed as ''Net contents 32 fl. oz. (1 qt.)''.

(4) A declaration of 1¾ quarts liquid measure shall be expressed as ''Net contents 56 fl. oz. (1 qt. 1½ pt.)'' or ''Net contents 56 fl. oz. (1 qt. 1 pt. 8 oz.)'' but not in terms of quart and ounce such as ''Net content 56 fl. oz. (1 qt. 24 oz.)''.

(5) A declaration of 2½ gallons liquid measure shall be expressed in the alternative as ''Net contents 2 gal. 2 qt.'' and not as ''2 gal. 4 pt.''

(n) For quantities, the following abbreviations and none other may be employed (periods and plural forms are optional):

weight wt.	gallon gal.
square sq.	quart qt.
fluid fl.	pint pt.
yard yd.	ounce oz.
feet or foot ft.	pound lb.
inch in.	

(o) On packages labeled in terms of linear measure, the declaration shall be expressed both in terms of inches and, if applicable (1 foot or more), the largest whole units (yards, yards and feet, feet). The declaration in terms of the largest whole units shall be in parentheses following the declaration in terms of inches and any remainder shall be in terms of inches or common or decimal fractions of the foot or yard. Examples are ''86 inches (2 yd. 1 ft. 2 inches)'', ''90 inches (2½ yd.)'', ''30 inches (2.5 ft.)'', etc.

(p) On packages labeled in terms of area measure, the declaration shall be expressed in terms of square inches and, if applicable (1 square foot or more), the largest whole square unit (square yards, square yards and square feet, square feet). The declaration in terms of the largest whole units shall be in parentheses following the declaration in terms of square inches and any remainder shall be in terms of square inches or common or decimal fractions of the square foot or square yard; for example, ''158 sq. inches (1 sq. ft. 14 sq. inches)'', etc.

(q) Nothing in this section shall prohibit supplemental statements at locations other than the principal display panel(s) describing in nondeceptive terms the net quantity of contents, provided that such supplemental statements of net quantity of contents shall not include any term qualifying a unit of weight, measure, or count that tends to exaggerate the amount of the cosmetic contained in the package; for example, ''giant pint'' and ''full quart.'' Dual or combination declarations of net quantity of contents as provided for in paragraphs (a), (c), and (j) of this section (for example, a combination of net weight plus numerical count) are not regarded as supplemental net quantity statements and shall be located on the principal display panel.

(r) A separate statement of the net quantity of contents in terms of the

metric system is not regarded as a supplemental statement and an accurate statement of the net quantity of contents in terms of the metric system of weight or measure may also appear on the principal display panel or on other panels.

(s) The declaration of net quantity of contents shall express an accurate statement of the quantity of contents of the package. Reasonable variations caused by loss or gain of moisture during the course of good distribution practice or by unavoidable deviations in good manufacturing practice will be recognized. Variations from stated quantity of contents shall not be unreasonably large.

Subpart C—Labeling of Specific Ingredients

§ 701.20 Detergent substances, other than soap, intended for use in cleansing the body.

(a) In its definition of the term ''cosmetic,'' the Federal Food, Drug, and Cosmetic Act specifically excludes soap. The term ''soap'' is nowhere defined in the act. In administering the act, the Food and Drug Administration interprets the term ''soap'' to apply only to articles that meet the following conditions:

(1) The bulk of the nonvolatile matter in the product consists of an alkali salt of fatty acids and the detergent properties of the article are due to the alkali-fatty acid compounds; and

(2) The product is labeled, sold, and represented only as soap.

(b) Products intended for cleansing the human body and which are not ''soap'' as set out in paragraph (a) of this section are ''cosmetics,'' and accordingly they are subject to the requirements of the act and the regulations thereunder. For example, such a product in bar form is subject to the requirement, among others, that it shall bear a label containing an accurate statement of the weight of the bar in avoirdupois pounds and ounces, this statement to be prominently and conspicuously displayed so as to be likely to be read under the customary conditions of purchase and use.

§ 701.30 Ingredient names established for cosmetic ingredient labeling.

The Commissioner establishes the following names for the purpose of cosmetic ingredient labeling pursuant to paragraph (e) of § 701.3:

Chemical name or description	Chemical formula	Established label name
Trichlorofluoromethane	CCl_3F	Chlorofluorocarbon 11.
Trichlorofluoromethane and 0.3 pct nitromethane	$CCl_3F+CH_3NO_2$	Chlorofluorocarbon 11 S.
Dichlorodifluoromethane	CCl_2F_2	Chlorofluorocarbon 12.
Chlorodifluoromethane	$CHClF_2$	Hydrochlorofluorocarbon 22.
1, 2-dichloro-1, 1, 2, 2-tetrafluoroethane	$CClF_2CClF_2$	Chlorofluorocarbon 114.
1-Chloro-1, 1-difluoroethane	CH_3CClF_2	Hydrochlorofluorocarbon 142 B.
1, 1-difluoroethane	CH_3CHF_2	Hydrofluorocarbon 152 A.
Ethyl ester of hydrolyzed animal protein is the ester of ethyl alcohol and the hydrolysate of collagen or other animal protein, derived by acid, enzyme, or other form of hydrolysis.		Ethyl ester of hydrolyzed animal protein.

[42 FR 24255, May 13, 1977, as amended at 45 FR 3577, Jan. 18, 1980]

PART 710—VOLUNTARY REGISTRATION OF COSMETIC PRODUCT ESTABLISHMENTS

Sec.

AUTHORITY: Secs. 201, 301, 601, 602, 701, 704 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, 331, 361, 362, 371, 374).

SOURCE: 39 FR 10059, Mar. 15, 1974, unless otherwise noted.

§ 710.1 Who should register.

The owner or operator of a cosmetic product establishment which is not

exempt under § 710.9 and engages in the manufacture or packaging of a cosmetic product is requested to register for each such establishment, whether or not the product enters interstate commerce. This request extends to any foreign cosmetic product establishment whose products are exported for sale in any State as defined in section 201(a)(1) of the act. No registration fee is required.

§ 710.2 Time for registration.

The owner or operator of an establishment entering into the manufacture or packaging of a cosmetic product should register his establishment within 30 days after the operation begins.

§ 710.3 How and where to register.

Form FD–2511 (''Registration of Cosmetic Product Establishment'') is obtainable on request from the Food and Drug Administration, Department of Health and Human Services, Washington, DC 20204, or at any Food and Drug Administration district office. The completed form should be mailed to Cosmetic Product Establishment Registration, Food and Drug Administration, Department of Health and Human Services, Washington, DC 20204.

§ 710.4 Information requested.

Form FD–2511 requests information on the name and address of the cosmetic product establishment, including post office ZIP code; all business trading names used by the establishment; and the type of business (manufacturer and/or packer). The information requested should be given separately for each establishment as defined in § 700.3(j) of this chapter.

[39 FR 10059, Mar. 15, 1974, as amended at 46 FR 38073, July 24, 1981; 54 FR 39640, Sept. 27, 1989]

§ 710.5 Amendments to registration.

Within 30 days after a change in any of the information contained on a submitted Form FD–2511, a new Form FD–2511 should be submitted to amend the registration. This amendment is also necessary when a registration is to be canceled because an establishment has changed its name and no longer conducts business under the original name.

§ 710.6 Notification of registrant; cosmetic product establishment registration number.

The Commissioner of Food and Drugs will provide the registrant with a validated copy of Form FD–2511 as evidence of registration. This validated copy will be sent only to the location shown for the registering establishment. A permanent registration number will be assigned to each cosmetic product establishment registered in accordance with the regulations in this part.

§ 710.7 Inspection of registrations.

A copy of the Form FD–2511 filed by the registrant will be available for inspection at the Food and Drug Administration, Department of Health and Human Services, Washington, DC 20204.

§ 710.8 Misbranding by reference to registration or to registration number.

Registration of a cosmetic product establishment or assignment of a registration number does not in any way denote approval of the firm or its products by the Food and Drug Administration. Any representation in labeling or advertising that creates an impression of official approval because of registration or possession of a registration number will be considered misleading.

§ 710.9 Exemptions.

The following classes of persons are not requested to register in accordance with this part 710 because the Commissioner has found that such registration is not justified:

(a) Beauty shops, cosmetologists, retailers, pharmacies, and other persons and organizations that compound cosmetic products at a single location and administer, dispense, or distribute them at retail from that location and who do not otherwise manufacture or package cosmetic products at that location.

(b) Physicians, hospitals, clinics, and public health agencies.

(c) Persons who manufacture, prepare, compound, or process cosmetic products solely for use in research,

pilot plant production, teaching, or chemical analysis, and who do not sell these products.

PART 720—VOLUNTARY FILING OF COSMETIC PRODUCT INGREDIENT AND COSMETIC RAW MATERIAL COMPOSITION STATEMENTS

Sec.

AUTHORITY: Secs. 201, 301, 601, 602, 701, 704 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, 331, 361, 362, 371, 374).

SOURCE: 39 FR 10060, Mar. 15, 1974, unless otherwise noted.

§ 720.1 Who should file.

Either the manufacturer, packer, or distributor of a cosmetic product is requested to file Form FDA 2512 (''Cosmetic Product Ingredient Statement''), whether or not the cosmetic product enters interstate commerce. This request extends to any foreign manufacturer, packer, or distributor of a cosmetic product exported for sale in any State as defined in section 201(a)(1) of the Federal Food, Drug, and Cosmetic Act. No filing fee is required.

[57 FR 3129, Jan. 28, 1992]

§ 720.2 Times for filing.

Within 180 days after forms are made available to the industry, Form FDA 2512 should be filed for each cosmetic product being commercially distributed as of the effective date of this part. Form FDA 2512 should be filed within 60 days after the beginning of commercial distribution of any product not covered within the 180-day period.

[57 FR 3129, Jan. 28, 1992]

§ 720.3 How and where to file.

Forms FDA 2512 and FDA 2514 (''Discontinuance of Commercial Distribution of Cosmetic Product Formulation'') are obtainable on request from the Food and Drug Administration, Department of Health and Human Services, Washington, DC 20204, or at any Food and Drug Administration district office. The completed form should be mailed or delivered to: Cosmetic Product Statement, Food and Drug Administration, Department of Health and Human Services, Washington, DC 20204, according to the instructions provided with the forms.

[57 FR 3129, Jan. 28, 1992]

§ 720.4 Information requested about cosmetic products.

(a) Form FDA–2512 requests information on:

(1) The name and address, including post office ZIP code of the person (manufacturer, packer, or distributor) designated on the label of the product.

(2) The name and address, including post office ZIP code, of the manufacturer or packer of the product if different from the person designated on the label of the product, when the manufacturer or packer submits the information requested under this paragraph.

(3) The brand name or names of the cosmetic product.

(4) The cosmetic product category or categories.

(5) The ingredients in the product.

(b) The person filing Form FDA–2512 should:

(1) Provide the information requested in paragraph (a) of this section.

(2) Have the form signed by an authorized individual.

(3) Provide poison control centers with ingredient information and/or adequate diagnostic and therapeutic procedures to permit rapid evaluation and treatment of accidental ingestion or other accidental use of the cosmetic product.

(4) Provide ingredient information (and, when requested, ingredient samples) to a licensed physician who, in connection with the treatment of a patient, requests assistance in determining whether an ingredient in the cosmetic product is the cause of the problem for which the patient is being treated.

(c) One or more of the following cosmetic product categories should be

cited to indicate the product's intended use.

(1) *Baby products.* (i) Baby shampoos.

(ii) Lotions, oils, powders, and creams.

(iii) Other baby products.

(2) *Bath preparations.* (i) Bath oils, tablets, and salts.

(ii) Bubble baths.

(iii) Bath capsules.

(iv) Other bath preparations.

(3) *Eye makeup preparations.* (i) Eyebrow pencil.

(ii) Eyeliner.

(iii) Eye shadow.

(iv) Eye lotion.

(v) Eye makeup remover.

(vi) Mascara.

(vii) Other eye makeup preparations.

(4) *Fragrance preparations.* (i) Colognes and toilet waters.

(ii) Perfumes.

(iii) Powders (dusting and talcum) (excluding aftershave talc).

(iv) Sachets.

(v) Other fragrance preparations.

(5) *Hair preparations (noncoloring).*

(i) Hair conditioners.

(ii) Hair sprays (aerosol fixatives).

(iii) Hair straighteners.

(iv) Permanent waves.

(v) Rinses (noncoloring).

(vi) Shampoos (noncoloring).

(vii) Tonics, dressings, and other hair grooming aids.

(viii) Wave sets.

(ix) Other hair preparations.

(6) *Hair coloring preparations.* (i) Hair dyes and colors (all types requiring caution statement and patch test).

(ii) Hair tints.

(iii) Hair rinses (coloring).

(iv) Hair shampoos (coloring).

(v) Hair color sprays (aerosol).

(vi) Hair lighteners with color.

(vii) Hair bleaches.

(viii) Other hair coloring preparations.

(7) *Makeup preparations (not eye).* (i) Blushers (all types).

(ii) Face powders.

(iii) Foundations.

(iv) Leg and body paints.

(v) Lipstick.

(vi) Makeup bases.

(vii) Rouges.

(viii) Makeup fixatives.

(ix) Other makeup preparations.

(8) *Manicuring preparations.* (i) Basecoats and undercoats.

(ii) Cuticle softeners.

(iii) Nail creams and lotions.

(iv) Nail extenders.

(v) Nail polish and enamel.

(vi) Nail polish and enamel removers.

(vii) Other manicuring preparations.

(9) *Oral hygiene products.* (i) Dentifrices (aerosol, liquid, pastes, and powders).

(ii) Mouthwashes and breath fresheners (liquids and sprays).

(iii) Other oral hygiene products.

(10) *Personal cleanliness.* (i) Bath soaps and detergents.

(ii) Deodorants (underarm).

(iii) Douches.

(iv) Feminine hygiene deodorants.

(v) Other personal cleanliness products.

(11) *Shaving preparations.* (i) Aftershave lotions.

(ii) Beard softeners.

(iii) Men's talcum.

(iv) Preshave lotions (all types).

(v) Shaving cream (aerosol, brushless, and lather).

(vi) Shaving soap (cakes, sticks, etc.).

(vii) Other shaving preparation products.

(12) *Skin care preparations, (creams, lotions, powder, and sprays).* (i) Cleansing (cold creams, cleansing lotions, liquids, and pads).

(ii) Depilatories.

(iii) Face and neck (excluding shaving preparations).

(iv) Body and hand (excluding shaving preparations).

(v) Foot powders and sprays.

(vi) Moisturizing.

(vii) Night.

(viii) Paste masks (mud packs).

(ix) Skin fresheners.

(x) Other skin care preparations.

(13) *Suntan preparations.* (i) Suntan gels, creams, and liquids.

(ii) Indoor tanning preparations.

(iii) Other suntan preparations.

(d) Ingredients in the product should be listed as follows:

(1) A list of each ingredient of the cosmetic product in descending order of predominance by weight (except that the fragrance and/or flavor may be designated as such without naming each individual ingredient when the manufacturer or supplier of the fragrance and/or flavor refuses to disclose ingredient data).

(2) An ingredient should be listed by the name adopted by the Food and Drug Administration (FDA) for the ingredient pursuant to §701.3(c) of this chapter.

(3) In the absence of a name adopted by FDA pursuant to §701.3(c) of this chapter, its common or usual name, if it has one, or its chemical or technical name should be listed.

(4) If an ingredient is a mixture, each ingredient of the mixture should be listed in accordance with paragraphs (d)(2) and (d)(3) of this section, unless such mixture is a formulation voluntarily registered on Form FDA 2512, in which case such mixture should be identified as ''fragrance,'' ''flavor,'' ''fragrance and flavor'' or ''base formulation,'' as appropriate, and by stating its FDA-assigned cosmetic product ingredient statement number.

(5) When the manufacturer or supplier of a fragrance and/or flavor refuses to disclose ingredient data, the fragrance and/or flavor should be listed as such. The nonconfidential listing of the product name and/or trade name or name of the manufacturer or supplier of each proprietary fragrance and/or flavor mixture is optional.

(e) A separate Form FDA–2512 should be filed for each different formulation of a cosmetic product. However, except for the hair coloring preparations listed in paragraph (c)(6) of this section for which a statement for each shade of such product is required, a single Form FDA–2512 may be filed for two or more shades of a cosmetic product where only the amounts of the color additive ingredient used are varied or in the case of flavors and fragrances where only the amounts of the flavors and fragrances used are varied.

(Information collection requirements in this section were approved by the Office of Management and Budget (OMB) and assigned OMB control number 0910–0030)

[39 FR 10060, Mar. 15, 1974, as amended at 46 FR 38073, July 24, 1981; 57 FR 3129, Jan. 28, 1992]

§ 720.5 [Reserved]

§ 720.6 Amendments to statement.

Changes in the information requested under §§720.4 (a)(3) and (a)(5) on the ingredients or brand name of a cosmetic product should be submitted by filing an amended Form FDA 2512 within 60 days after the product is entered into commercial distribution. Other changes do not justify immediate amendment, but should be shown by filing an amended Form FDA 2512 within a year after such changes. Notice of discontinuance of commercial distribution of a cosmetic product formulation should be submitted by Form FDA 2514 within 180 days after discontinuance of commercial distribution becomes known to the person filing.

(Information collection requirements in this section were approved by the Office of Management and Budget (OMB) and assigned OMB control number 0910–0030)

[57 FR 3130, Jan. 28, 1992]

§ 720.7 Notification of person submitting cosmetic product ingredient statement.

When Form FDA 2512 is received, FDA will either assign a permanent cosmetic product ingredient statement number or a Food and Drug Administration (FDA) reference number in those cases where a permanent number cannot be assigned. Receipt of the form will be acknowledged by sending the individual signing the statement an appropriate notice bearing either the FDA reference number or the permanent cosmetic product ingredient statement number. If the person submitting Form FDA 2512 has not complied with §§720.4 (b)(1) and (b)(2), the person will be notified as to the manner in which the statement is incomplete.

[57 FR 3130, Jan. 28, 1992]

§ 720.8 Confidentiality of statements.

(a) Data and information contained in, attached to, or included with Forms FDA 2512 and FDA 2514, and amendments thereto are submitted voluntarily to the Food and Drug Administration (FDA). Any request for confidentiality of a cosmetic ingredient submitted with such forms or separately will be handled in accordance with the procedure set forth in this section and in §20.44 of this chapter. The request for confidentiality will also be subject to the provisions of §20.111 of this chapter, as well as to the

exemptions in subpart D of part 20 of this chapter and to the limitations on exemption in subpart E of part 20 of this chapter.

(b) Any request for confidentiality of the identity of a cosmetic ingredient should contain a full statement, in a well-organized format, of the factual and legal grounds for that request, including all data and other information on which the petitioner relies, as well as representative information known to the petitioner that is unfavorable to the petitioner's position. The statement of the factual grounds should include, but should not be limited to, scientific or technical data, reports, tests, and other relevant information addressing the following factors that FDA will consider in determining whether the identity of an ingredient qualifies as a trade secret:

(1) The extent to which the identity of the ingredient is known outside petitioner's business;

(2) The extent to which the identity of the ingredient is known by employees and others involved in petitioner's business;

(3) The extent of measures taken by the petitioner to guard the secrecy of the information;

(4) The value of the information about the identity of the claimed trade secret ingredient to the petitioner and to its competitors;

(5) The amount of effort or money expended by petitioner in developing the ingredient; and

(6) The ease or difficulty with which the identity of the ingredient could be properly acquired or duplicated by others.

(c) The request for confidentiality should also be accompanied by a statement that the identity of the ingredient for which confidentiality is requested has not previously been published or disclosed to anyone other than as provided in §20.81(a) of this chapter.

(d) FDA will return to the petitioner any request for confidentiality that contains insufficient data to permit a review of the merits of the request. FDA will also advise the petitioner about the additional information that is necessary to enable the agency to proceed with its review of the request.

(e) If, after receiving all of the data that are necessary to make a determination about whether the identity of an ingredient is a trade secret, FDA tentatively decides to deny the request, the agency will inform the person requesting trade secrecy of its tentative determination in writing. FDA will set forth the grounds upon which it relied in making this tentative determination. The petitioner may withdraw the records for which FDA has tentatively denied a request for confidentiality or may submit, within 60 days from the date of receipt of the written notice of the tentative denial, additional relevant information and arguments and request that the agency reconsider its decision in light of both the additional material and the information that it originally submitted.

(f) If the petitioner submits new data in response to FDA's tentative denial of trade secret status, the agency will consider that material together with the information that was submitted initially before making its final determination.

(g) A final determination that an ingredient is not a trade secret within the meaning of §20.61 of this chapter constitutes final agency action that is subject to judicial review under 5 U.S.C. Chapter 7. If suit is brought within 30 calendar days after such a determination, FDA will not disclose the records involved or require that the disputed ingredient or ingredients be disclosed in labeling until the matter is finally determined in the courts. If suit is not brought within 30 calendar days after a final determination that an ingredient is not a trade secret within the meaning of 21 CFR 20.61, and the petitioner does not withdraw the records for which a request for confidentiality has been denied, the records involved will be made a part of FDA files and will be available for public disclosure upon request.

[51 FR 11444, Apr. 3, 1986, as amended at 57 FR 3130, Jan. 28, 1992]

§720.9 Misbranding by reference to filing or to statement number.

The filing of Form FDA 2512 or assignment of a number to the statement does not in any way denote approval by the Food and Drug Administration of

the firm or the product. Any representation in labeling or advertising that creates an impression of official approval because of such filing or such number will be considered misleading.

[57 FR 3130, Jan. 28, 1992]

PART 730—VOLUNTARY FILING OF COSMETIC PRODUCT EXPERIENCES

Sec.

AUTHORITY: Secs. 201, 301, 601, 602, 701, 704 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, 331, 361, 362, 371, 374).

SOURCE: 39 FR 10062, Mar. 15, 1974, unless otherwise noted.

§ 730.1 Who should file.

Every person who is a manufacturer, packer, or distributor of a cosmetic product is requested to file a Form FD–2704 (Cosmetic Product Experience Report), with respect to all reportable experiences which have been reported to him concerning any of his cosmetic products in commercial distribution, regardless of whether he is a participant in the voluntary program to register cosmetic product establishments pursuant to part 710 of this chapter, and regardless of whether he is a participant in the voluntary program to file cosmetic product ingredient and raw material composition statements pursuant to part 720 of this chapter. In addition, every person who is a manufacturer, packer, or distributor of a cosmetic product, whether or not he has received any information concerning a reportable experience in regard to any of his cosmetic products in his system of commercial distribution, is requested to file a Form FD–2706 (Summary Report of Cosmetic Product Experience by Product Categories). This request extends to any foreign manufacturer, packer, or distributor of a cosmetic product imported into any State. No filing fee is required.

[39 FR 10062, Mar. 15, 1974, as amended at 46 FR 38073, July 24, 1981]

§ 730.2 Time for filing.

(a) Reportable experiences should be reported on an annual basis, for the period January through December, not later than 60 days after the close of the reporting period.

(b) A summary report of cosmetic product experience by product categories should be filed on an annual basis, for the period January through December, not later than 60 days after the close of the reporting period.

[51 FR 25687, July 16, 1986]

§ 730.3 How and where to file.

Form FDA 2704 (Cosmetic Product Experience Report) and Form FDA 2706 (Summary Report of Cosmetic Product Experience by Product Categories) are obtainable from, and the completed forms should be mailed or delivered to, Cosmetic Product Experience Report, Center for Food Safety and Applied Nutrition (HFS–100), Food and Drug Administration, 200 C St. SW., Washington, DC 20204.

[51 FR 25687, July 16, 1986, as amended at 61 FR 14481, Apr. 2, 1996]

§ 730.4 Information requested.

(a) Form FD–2704 (Cosmetic Product Experience Report) requests the following information:

(1) The name of the person (manufacturer, packer, or distributor) designated on the label of the cosmetic product.

(2) Time period covered by the report.

(3) The complete name of the cosmetic product exactly as it appears on the label of the product.

(4) The cosmetic product category, as set forth in §720.4(c) of this chapter and on the form, which best describes the product's intended use.

(5) Total number of reportable experiences during this reporting period and number of these experiences requiring professional medical attention.

(6) Total number of product units of the cosmetic product estimated to have been distributed to consumers during this reporting period.

(7)–(8) [Reserved]

(9) The cosmetic product ingredient statement number (CPIS No.) assigned to the product under § 720.7 of this chapter, if known. If a number is pending, but has not been assigned, the firm should so indicate. Where the firm submitting the report knows that a cosmetic product ingredient statement pursuant to part 720 of this chapter has not been filed, it should so indicate.

(10) Any additional evaluation of the experiences or other pertinent data or information as the person filing wishes to provide to assist the Food and Drug Administration in evaluating the report.

(b) [Reserved]

(c) Form FD–2706 (Summary Report of Cosmetic Product Experience by Product Categories) requests the following information:

(1) The name and address (include country, if other than the United States), including post office ZIP code of the person (manufacturer, packer, or distributor) designated on the label of the cosmetic products.

(2) Time period covered by the report.

(3) Total number of product units within each product category, as set forth in § 720.4(c) of this chapter and on the form, estimated to have been distributed to consumers during this reporting period.

(4) Total number of reportable experiences within each product category during this reporting period, if any.

(d) The person filing a Form FD–2704 (Cosmetic Product Experience Report)or Form FD–2706 (Summary Report of Product Experience by Product Categories) should:

(1) Provide the information requested in paragraphs (a) and (c) of this section, as appropriate.

(2) Provide the screening procedure in conformance with § 700.3(p) when a screening procedure is used in connection with the reports requested by this part and is not already on file with the Food and Drug Administration.

(3) Provide the name, title, and signature of the individual authorized to submit the report(s), and the name and address of the firm which he represents if it differs from that provided in paragraph (a) or (c) of this section.

(e) The information requested under paragraph (a) of this section should be filed separately for each cosmetic product, except that a single report may be filed for two or more shades, flavors, or fragrances of a cosmetic product where only the proportions of these ingredients are varied, and such product is covered by a single cosmetic product ingredient statement under § 720.4(e) of this chapter.

(f) On the basis of a review of individual reports or patterns of experience disclosed as a result of a number of reports, the Commissioner of Food and Drugs may request as much additional information from persons submitting reports as the Commissioner deems appropriate. For this reason, every person participating in this program should retain for three years all correspondence and records pertaining to alleged cosmetic product injuries.

[39 FR 10062, Mar. 15, 1974, as amended at 46 FR 38074, July 24, 1981; 51 FR 25687, July 16, 1986]

§ 730.5 Additions or amendments to reports.

Additions or amendments to any experience report should be submitted by filing the appropriate amended form as soon as the need for such additions or amendments becomes apparent to the person submitting the original report.

§ 730.6 Notification to person submitting reports.

Anyone desiring a receipt for information submitted should send it by registered mail requesting a return receipt.

§ 730.7 Confidentiality of reports.

The availability for public disclosure of all data and information contained in, attached to, or included with Forms FD–2704, 2706, and amendments thereto, shall be handled in accordance with the provisions established in part 20 of this chapter. All such data and information are submitted voluntarily to the Food and Drug Administration and are thus subject to the specific provisions concerning data and information submitted voluntarily to the Food and Drug Administration in § 20.111 of this chapter, as well as to the exemptions in subpart D of part 20 of this chapter and

the limitations on exemptions in subpart E of part 20 of this chapter.

[39 FR 44657, Dec. 24, 1974, as amended at 42 FR 15676, Mar. 22, 1977; 46 FR 38074, July 24, 1981]

§ 730.8 Misbranding by reference to filing; filing does not constitute an admission.

(a) The filing of an experience report does not in any way denote approval of the firm or the cosmetic product by the Food and Drug Administration. Any representation in labeling or advertising that creates an impression of official approval because of such filing will be considered misleading.

(b) The filing of an experience report does not in any way constitute an admission by the person filing the report that the alleged experience was the result of an ingredient or ingredients in the cosmetic product, or of any other fact.

PART 740—COSMETIC PRODUCT WARNING STATEMENTS

Subpart A—General

Sec.

Subpart B—Warning Statements

AUTHORITY: Secs. 201, 301, 502, 505, 601, 602, 701, 704 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, 331, 352, 355, 361, 362, 371, 374).

Subpart A—General

§ 740.1 Establishment of warning statements.

(a) The label of a cosmetic product shall bear a warning statement whenever necessary or appropriate to prevent a health hazard that may be associated with the product.

(b) The Commissioner of Food and Drugs, either on his own initiative or on behalf of any interested person who has submitted a petition, may publish a proposal to establish or amend, under subpart B of this part, a regulation prescribing a warning for a cosmetic. Any such petition shall include an adequate factual basis to support the petition, shall be in the form set forth in part 10 of this chapter, and will be published for comment if it contains reasonable grounds for the proposed regulation.

[40 FR 8917, Mar. 3, 1975, as amended at 42 FR 15676, Mar. 22, 1977]

§ 740.2 Conspicuousness of warning statements.

(a) A warning statement shall appear on the label prominently and conspicuously as compared to other words, statements, designs, or devices and in bold type on contrasting background to render it likely to be read and understood by the ordinary individual under customary conditions of purchase and use, but in no case may the letters and/or numbers be less than 1/16 inch in height, unless an exemption pursuant to paragraph (b) of this section is established.

(b) If the label of any cosmetic package is too small to accommodate the information as required by this section, the Commissioner may establish by regulation an acceptable alternative method, e.g., type size smaller than 1/16 inch in height. A petition requesting such a regulation, as an amendment to this section, shall be submitted to the Dockets Management Branch in the form established in part 10 of this chapter.

[40 FR 8917, Mar. 3, 1975, as amended at 42 FR 15676, Mar. 22, 1977]

Subpart B—Warning Statements

§ 740.10 Labeling of cosmetic products for which adequate substantiation of safety has not been obtained.

(a) Each ingredient used in a cosmetic product and each finished cosmetic product shall be adequately substantiated for safety prior to marketing. Any such ingredient or product whose safety is not adequately substantiated prior to marketing is

misbranded unless it contains the following conspicuous statement on the principal display panel:

Warning—The safety of this product has not been determined.

(b) An ingredient or product having a history of use in or as a cosmetic may at any time have its safety brought into question by new information that in itself is not conclusive. The warning required by paragraph (a) of this section is not required for such an ingredient or product if:

(1) The safety of the ingredient or product had been adequately substantiated prior to development of the new information;

(2) The new information does not demonstrate a hazard to human health; and

(3) Adequate studies are being conducted to determine expeditiously the safety of the ingredient or product.

(c) Paragraph (b) of this section does not constitute an exemption to the adulteration provisions of the Act or to any other requirement in the Act or this chapter.

[40 FR 8917, Mar. 3, 1975]

§ 740.11 Cosmetics in self-pressurized containers.

(a)(1) The label of a cosmetic packaged in a self-pressurized container and intended to be expelled from the package under pressure shall bear the following warning:

Warning—Avoid spraying in eyes. Contents under pressure. Do not puncture or incinerate. Do not store at temperature above 120° F. Keep out of reach of children.

(2) In the case of products intended for use by children, the phrase ''except under adult supervision'' may be added at the end of the last sentence in the warning required by paragraph (a)(1) of this section.

(3) In the case of products packaged in glass containers, the word ''break'' may be substituted for the word ''puncture'' in the warning required by paragraph (a)(1) of this section.

(4) The words ''Avoid spraying in eyes'' may be deleted from the warning required by paragraph (a)(1) of this section in the case of a product not expelled as a spray.

(b)(1) In addition to the warning required by paragraph (a)(1) of this section, the label of a cosmetic packaged in a self-pressurized container in which the propellant consists in whole or in part of a halocarbon or a hydrocarbon shall bear the following warning:

Warning—Use only as directed. Intentional misuse by deliberately concentrating and inhaling the contents can be harmful or fatal.

(2) The warning required by paragraph (b)(1) of this section is not required for the following products:

(i) Products expelled in the form of a foam or cream, which contain less than 10 percent propellant in the container.

(ii) Products in a container with a physical barrier that prevents escape of the propellant at the time of use.

(iii) Products of a net quantity of contents of less than 2 ozs. that are designed to release a measured amount of product with each valve actuation.

(iv) Products of a net quantity of contents of less than ½ oz.

(c)(1) In addition to the warnings required by paragraphs (a)(1) and (b)(1) of this section, the label on each package of a cosmetic in a self-pressurized container in which the propellant consists in whole or in part of a fully halogenated chlorofluoroalkane (chlorofluorocarbon) shall bear the following warning:

Warning—Contains a chlorofluorocarbon that may harm the public health and environment by reducing ozone in the upper atmosphere.

(2) The warning required by paragraph (c)(1) of this section shall appear on an appropriate panel with such prominence and conspicuousness as to render it likely to be read and understood by ordinary individuals under normal conditions of purchase. The warning may appear on a firmly affixed tag, tape, card, or sticker or similar overlabeling attached to the package. The warning shall comply in all other respects with § 740.2, e.g., type-size requirements.

(3) The warning required by paragraph (c)(1) of this section is applicable only to self-pressurized containers that use a chlorofluorocarbon in whole or in part as a propellant to expel from the

container liquid or solid material different from the propellant.

[40 FR 8917, Mar. 3, 1975, as amended at 42 FR 22033, Apr. 29, 1977; 54 FR 39640, Sept. 27, 1989]

§ 740.12 Feminine deodorant sprays.

(a) For the purpose of this section, the term ''feminine deodorant spray'' means any spray deodorant product whose labeling represents or suggests that the product is for use in the female genital area or for use all over the body.

(b) The label of a feminine deodorant spray shall bear the following statement:

Caution—For external use only. Spray at least 8 inches from skin. Do not apply to broken, irritated, or itching skin. Persistent, unusual odor or discharge may indicate conditions for which a physician should be consulted. Discontinue use immediately if rash, irritation, or discomfort develops.

The sentence ''Spray at least 8 inches from skin'' need not be included in the cautionary statement for products whose expelled contents do not contain a liquified gas propellant such as a halocarbon or hydrocarbon propellant.

(c) Use of the word ''hygiene'' or ''hygienic'' or a similar word or words renders any such product misbranded under section 602(a) of the Federal Food, Drug, and Cosmetic Act. The use of any word or words which represent or suggest that such products have a medical usefulness renders such products misbranded under section 502(a) of the Act and illegal new drugs marketed in violation of section 505 of the Act.

[40 FR 8929, Mar. 3, 1975]

§ 740.17 Foaming detergent bath products.

(a) For the purpose of this section, a foaming detergent bath product is any product intended to be added to a bath for the purpose of producing foam that contains a surface-active agent serving as a detergent or foaming ingredient.

(b) The label of foaming detergent bath products within the meaning of paragraph (a) of this section, except for those products that are labeled as intended for use exclusively by adults, shall bear adequate directions for safe use and the following caution:

Caution—Use only as directed. Excessive use or prolonged exposure may cause irritation to skin and urinary tract. Discontinue use if rash, redness, or itching occurs. Consult your physician if irritation persists. Keep out of reach of children.

(c) In the case of products intended for use by children, the phrase ''except under adult supervision'' may be added at the end of the last sentence in the caution required by paragraph (b) of this section.

[51 FR 20475, June 5, 1986]

§ 740.18 Coal tar hair dyes posing a risk of cancer.

(a) The principal display panel of the label and any labeling accompanying a coal tar hair dye containing any ingredient listed in paragraph (b) of this section shall bear, in accordance with the requirements of § 740.2, the following:

Warning—Contains an ingredient that can penetrate your skin and has been determined to cause cancer in laboratory animals.

(b) Hair dyes containing any of the following ingredients shall comply with the requirements of this section: (1) 4-methoxy-*m*-phenylenediamine (2,4-diaminoanisole) and (2) 4-methoxy-*m*-phenylenediamine sulfate (2,4-diaminoanisole sulfate).

[44 FR 59522, Oct. 16, 1979]

EFFECTIVE DATE NOTE: At 47 FR 7829, Feb. 23, 1982, the effectiveness of § 740.18 was stayed until further notice. The stay was effective Sept. 18, 1980.

PARTS 741—799 [RESERVED]

FINDING AIDS

A list of CFR titles, subtitles, chapters, subchapters and parts and an alphabetical list of agencies publishing in the CFR are included in the CFR Index and Finding Aids volume to the Code of Federal Regulations which is published separately and revised annually.

Material Approved for Incorporation by Reference

(Revised as of April 1, 1996)

The Director of the Federal Register has approved under 5 U.S.C. 552(a) and 1 CFR Part 51 the incorporation by reference of the following publications. This list contains only those incorporations by reference effective as of the revision date of this volume. Incorporations by reference found within a regulation are effective upon the effective date of that regulation. For more information on incorporation by reference, see the preliminary pages of this volume.

21 CFR CHAPTER I (PARTS 600 TO 799)
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	21 CFR
Cosmetic, Toiletry, and Fragrance Association, Inc. 1133 15th St. NW., Washington, DC 20065.	
Cosmetic, Toiletry, and Fragrance Association, Inc., Cosmetic Ingredient Dictionary, Second Ed., 1977.	701.3(c)(2)(i).
National Academy of Sciences, National Research Council 2101 Constitution Ave. NW., Washington, DC 20037.	
Food Chemicals Codex, 2nd Ed., 1972	720.4(d)
Food Chemicals Codex, 2nd Ed., 1972, First Supplement, 1974	701.3(c)
Food Chemicals Codex, 2nd Ed., 1972, Second Supplement, 1975	701.3(c)(2)(iv)

NOTE: The following materials are available through the Food and Drug Administration at the addresses indicated.

Bureau of Biologics, Food and Drug Administration 8800 Rockville Pike, Bethesda, MD 20205	
Standard Methods for the Examination of Water and Waste Water, 13th Ed..	630.74
United States Pharmacopeial Covention, Inc. 12601 Twinbrook Parkway, Rockville, MD 20852	
United States Pharmacopeia (21st revision, 1985)	
Test Procedures Using Membrane Filtration, p. 1159	610.12(f)

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601 Authority citation revised 15607
601.25 (d)(2) amended 15607
610 Authority citation revised 15607, 37450, 44453, 44906
610.9 (b) amended 15607
610.11 Introductory text, (c) introductory text, (2), and (3) amended 15607
610.12 (a)(1)(i), (e)(2), (f), and (g)(2) and (8) revised; (h) added 44906
610.15 (a) introductory text amended 15607
610.18 (c) and (d) added; OMB number 44453
610.40 (b)(4), (d)(1)(v) and (2)(iv) amended 15607
610.53 (c) table revised 15607
(c) table corrected 19750
(c) table amended 37450
620 Authority citation revised 15610
620.6 (h) amended 15610
620.12 Introductory text amended 15610
620.14 (c) introductory text amended 15610
620.24 (c) introductory text amended 15610

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620.35 (e) introductory text amended 15610
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630 Authority citation revised 15610
630.5 (c) introductory text amended 15610
(c) introductory text corrected 18580
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630.16 (a)(6) amended 15610
630.17 (e) introductory text amended 15610
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630.56 (f) introductory text amended 15610
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630.86 (e) introductory text amended 15611
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640.30 Amendments at 50 FR 4139 effective date deferred to 9–2–86 3773
640.50 Amendments at 50 FR 4139 effective date deferred to 9–2–86 3773
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640.111 (g) introductory text amended 15611
650 Authority citation revised 15611
650.11 (c) introductory text amended 15611
660 Authority citation revised 15611
660.6 (a)(2) amended 15611
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660.101 Introductory text amended 15611
660.102 Introductory text amended 39637
660.103 (f)(1) revised 39637
660.105 (a) introductory text amended 15611
(a)(1) revised 39637
680 Authority citation revised 15611
680.3 (e) and (f) added; OMB number 37607
680.4 (c)(1) introductory text amended 15611
Removed 37607
680.21 Amended 15611
680.26 Amended 15611

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720.8 Revised 11444
730 Authority citation revised; section authority citations removed 25687
730.2 Revised 25687
730.3 Revised 25687
730.4 (a)(1) revised 25687
740 Authority citation revised 20475
740.17 Revised; eff. 6–5–87 20475

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610 Authority citation revised 37450
610.53 (c) table amended 37450
660.30–660.36 (Subpart D) Revised; eff. in part 10–7–88 37450
660.102 Introductory text amended 39637
660.103 (f)(1) revised 39637
660.105 (a)(1) revised 39637
680.3 (e) and (f) added; OMB number 37607
680.4 Removed 37607

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606.122 (e) revised 116
610 Authority citation revised 116
610.12 (g)(4)(i) revised 12764
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