

(c) *Additives in source material.* The source material shall contain no additives other than citrate or acid citrate dextrose anticoagulant solution, unless it is shown that the processing method yields a product free of the additive to such an extent that the safety, purity, and potency of the product will not be affected adversely.

[38 FR 32089, Nov. 20, 1973, as amended at 50 FR 4140, Jan. 29, 1985; 64 FR 26287, May 14, 1999]

#### § 640.101 General requirements.

(a) *Heat stability test.* Approximately 2 ml. of completely processed material of each lot shall not show any visible sign of gelation after heating in a 12x75 mm. stoppered glass tube at 57 °C for 4 hours.

(b) *pH.* The pH of final container material shall be 6.8 ±0.4 when measured in a solution diluted to 1 percent protein with 0.15 molar sodium chloride.

(c) *Turbidity.* The product shall be free of turbidity as determined by visual inspection of final containers.

(d) *Date of manufacture.* The date of manufacture is the date of initiating the last valid measles or poliomyelitis antibody test (§ 640.104(b) (2) and (3)) whichever date is earlier.

(e) *Labeling.* In addition to complying with all applicable labeling required in this subchapter, labeling shall indicate that:

(1) There is no prescribed potency for viral hepatitis antibodies.

(2) The product is not recommended for intravenous administration.

[38 FR 32089, Nov. 20, 1973; 48 FR 13026, Mar. 29, 1983, as amended at 49 FR 23834, June 8, 1984; 50 FR 4140, Jan. 29, 1985; 51 FR 15611, Apr. 25, 1986; 55 FR 11013, Mar. 26, 1990; 63 FR 16685, Apr. 6, 1998; 64 FR 26287, May 14, 1999]

#### § 640.102 Manufacture of Immune Globulin (Human).

(a) *Processing method.* The processing method shall be one that has been shown: (1) To be capable of concentrating tenfold from source material at least two different antibodies; (2) not to affect the integrity of the globulins; (3) to consistently yield a product which is safe for subcutaneous and intramuscular injection and (4) not to transmit viral hepatitis.

(b) *Microbial contamination.* Low temperatures or aseptic techniques shall be used to minimize contamination by microorganisms. Preservatives to inhibit growth of microorganisms shall not be used during processing.

(c) *Bulk storage.* The globulin fraction may be stored in bulk prior to further processing provided it is stored in clearly identified hermetically closed vessels. Globulin as either a liquid concentrate or a solid and containing alcohol or more than 5 percent moisture shall be stored at a temperature of -10 °C or lower. Globulin as a solid free from alcohol and containing less than 5 percent moisture, shall be stored at a temperature of 0 °C or lower.

(d) *Determination of the lot.* Each lot of Immune Globulin (Human) shall represent a pooling of approximately equal amounts of material from not less than 1,000 donors.

(e) *Sterilization and heating.* The final product shall be sterilized promptly after solution. At no time during processing shall the product be exposed to temperatures above 45 °C, and after sterilization the product shall not be exposed to temperatures above 32 °C for more than 72 hours.

[38 FR 32089, Nov. 20, 1973, as amended at 50 FR 4140, Jan. 29, 1985; 63 FR 16685, Apr. 6, 1998; 64 FR 26287, May 14, 1999; 65 FR 13679, Mar. 14, 2000; 65 FR 52018, Aug. 28, 2000]

#### § 640.103 The final product.

(a) *Final solution.* The final product shall be a 16.5 ±1.5 percent solution of globulin containing 0.3 molar glycine and a preservative.

(b) *Protein composition.* At least 96 percent of the total protein shall be immunoglobulin G (IgG), as determined by a method that has been approved for each manufacturer by the Director, Center for Biologics Evaluation and Research, Food and Drug Administration.

[38 FR 32089, Nov. 20, 1973, as amended at 64 FR 26287, May 14, 1999]

#### § 640.104 Potency.

(a) *Antibody levels and tests.* Each lot of final product shall contain at least the minimum levels of antibodies for diphtheria, measles, and for at least one type of poliomyelitis. In the event the final bulk solution is stored at a

**§ 640.120**

temperature above 5 °C the antibody level tests shall be performed after such storage with a sample of the stored material.

(b) *Minimum levels.* The minimum antibody levels are as follows:

(1) No less than 2 units of diphtheria antitoxin per ml.

(2) A measles neutralizing antibody level that, when compared with that of a reference material designated by the Center for Biologics Evaluation and Research (CBER), Food and Drug Administration, as indicated in paragraph (c) of this section, demonstrates adequate potency. The Director, CBER, shall notify manufacturers when a new reference material will be used and will advise manufacturers of an appropriate antibody level taking into account a comparison of the new reference material to the previous reference material.

(3) A poliomyelitis Type 1, Type 2, or Type 3 neutralizing antibody level that, when compared with that of a reference material designated by the Center for Biologics Evaluation and Research, Food and Drug Administration, as indicated in paragraph (c) of this section, demonstrates adequate potency. The Director, CBER, shall notify manufacturers when a new reference material will be used and will advise manufacturers of an appropriate antibody level taking into account a comparison of the new reference material to the previous reference material.

(c) *Reference materials.* The following reference materials shall be obtained from the Center for Biologics Evaluation and Research:

(1) Reference Immune Globulin for correlation of measles antibody titers.

(2) Reference Immune Globulin for correlation of poliomyelitis antibody titers, Types 1, 2, and 3.

[38 FR 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; 63 FR 16685, Apr. 6, 1998; 64 FR 26287, May 14, 1999]

**Subpart K [Reserved]**

**Subpart L—Alternative Procedures**

**§ 640.120 Alternative procedures.**

(a) The Director, Center for Biologics Evaluation and Research, may approve

**21 CFR Ch. I (4–1–13 Edition)**

an exception or alternative to any requirement in subchapter F of chapter I of title 21 of the Code of Federal Regulations regarding blood, blood components, or blood products. Requests for such exceptions or alternatives shall ordinarily be in writing. Licensed establishments shall submit such requests in accordance with §601.12 of this chapter. However, in limited circumstances, such requests may be made orally and permission may be given orally by the Director. Oral requests and approvals must be promptly followed by written requests and written approvals.

(b) FDA will publish a list of approved alternative procedures and exceptions periodically in the FEDERAL REGISTER.

[55 FR 10423, Mar. 21, 1990, as amended at 62 FR 39903, July 24, 1997]

**PART 660—ADDITIONAL STANDARDS FOR DIAGNOSTIC SUBSTANCES FOR LABORATORY TESTS**

**Subpart A—Antibody to Hepatitis B Surface Antigen**

Sec.

- 660.1 Antibody to Hepatitis B Surface Antigen.
- 660.2 General requirements.
- 660.3 Reference panel.
- 660.4 Potency test.
- 660.5 Specificity.
- 660.6 Samples; protocols; official release.

**Subpart B [Reserved]**

**Subpart C—Blood Grouping Reagent**

- 660.20 Blood Grouping Reagent.
- 660.21 Processing.
- 660.22 Potency requirements with reference preparations.
- 660.25 Potency tests without reference preparations.
- 660.26 Specificity tests and avidity tests.
- 660.28 Labeling.

**Subpart D—Reagent Red Blood Cells**

- 660.30 Reagent Red Blood Cells.
- 660.31 Suitability of the donor.
- 660.32 Collection of source material.
- 660.33 Testing of source material.
- 660.34 Processing.
- 660.35 Labeling.
- 660.36 Samples and protocols.